BODY WEIGHT HOMEOSTASIS

PROFESSOR SUZANNE L DICKSON

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Measuring obesity and obesity statistics

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BODY MASS INDEX (kg/m^2)

DEFINITIONS
Overweight and obesity are defined as **abnormal or excessive fat accumulation that presents a risk to health**.

ADULTS: A body mass index (BMI) over 25 is considered overweight and over 30 is obese.

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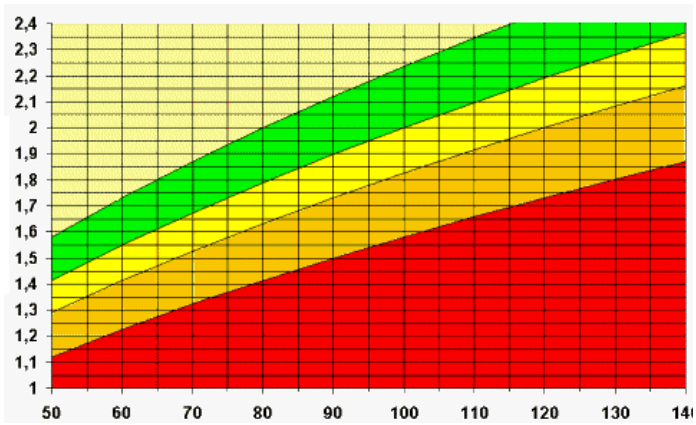
BMI for adults



BMI
- Normal 20-25
- Overweight >25
- Obese >30
- Morbidly Obese >40

Body mass index (BMI) = weight/height^2 (**kg/m^2**)

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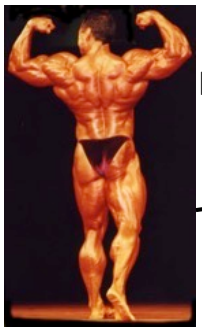
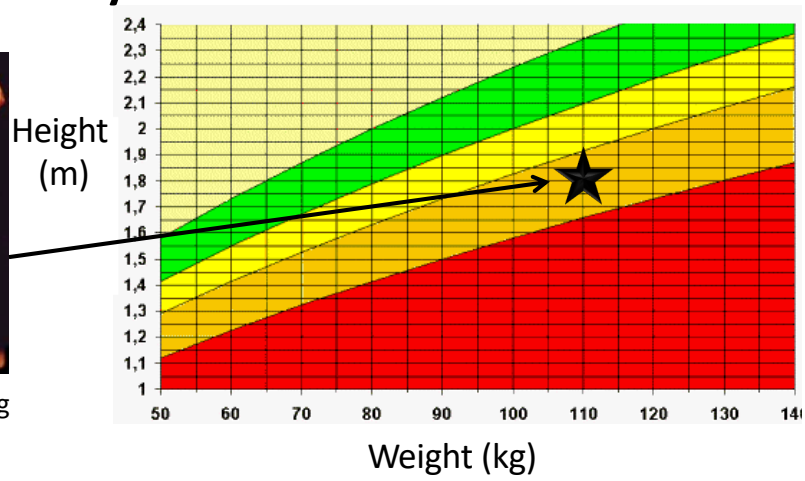
A cautionary note …..



Weight: 110 Kg
Height: 1.8 m
→ BMI: 34



BMI

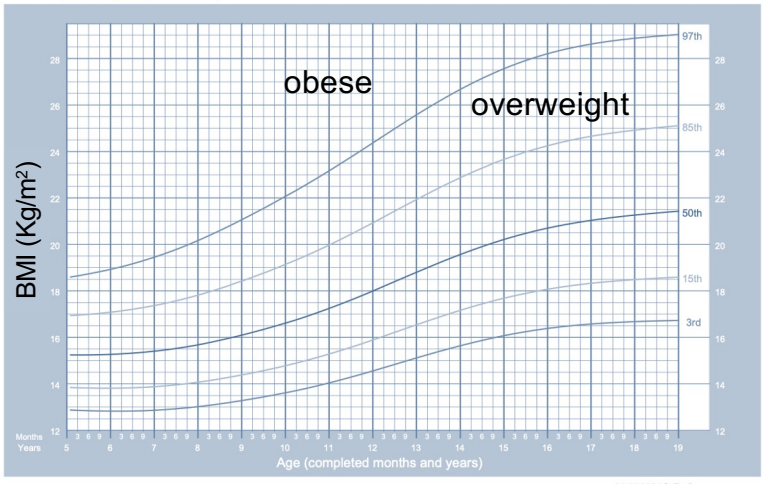
- Normal 20-25
- Overweight >25
- Obese >30
- Morbidly Obese >40

This calculation does not predict obesity for body builders (muscle) or for those that are very tall

BMI-for-Age GIRLS

World Health Organization

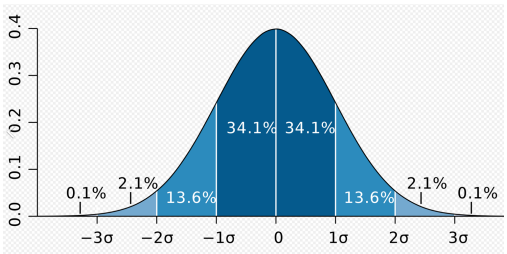
5 to 19 years (percentiles)



2007 WHO Reference

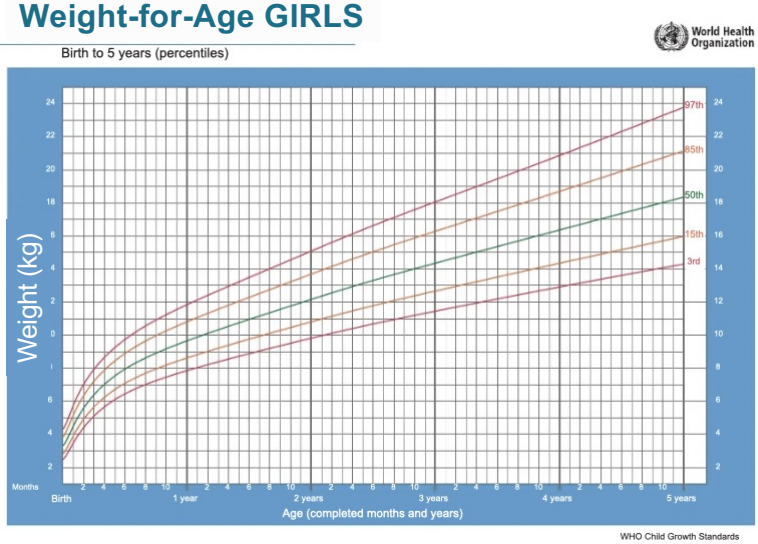
5 ← Age → 19 yrs

Age 5-19:
Use BMI-for-age
Overweight : >1 standard deviation above the growth reference mean
Obesity: >2 standard deviations above the growth reference mean



Weight-for-Age GIRLS

Birth to 5 years (percentiles)

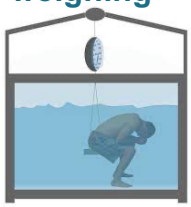


Age <5
Use Weight-for-age
Overweight: >2 standard deviations above the growth reference mean
Obesity: >3 standard deviations above the growth reference mean

Birth ⟵ Age ⟶ 5 yrs

Direct methods for assessing fat mass

Underwater weighing

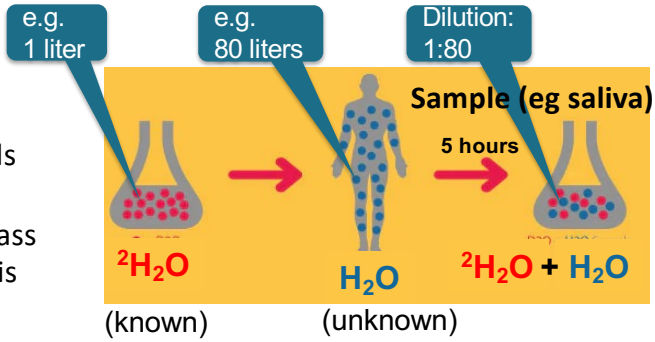


Accurate. Was gold standard before more advanced methods. Fat *vs* non-fat tissue have different densities.

Whole-Body (ADP)
Air Displacement Plethysmography

Like underwater weighing – displace air instead of water.

Total body water (TBW). Drink deuterated (or tritiated) water → ends up in the fat-free compartment → sampling gives TBW. From this, fat mass can be calculated (since body weight is known).



Direct methods for assessing fat mass

Dual X-Ray absorptiometry (DEXA)

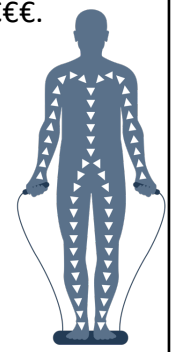
X-rays of two different energies. One absorbed more strongly by fat. Subtract one image from the other → amount of fat relative to other tissues at each point. Measures total fat and gives distribution. €€€. Involves exposure to (low level) radiation. OFTEN USED IN RESEARCH.

Computerized tomography

Cross-sectional radiographs of abdomen → computerized measurement of total fat area and regional fat determination (e.g. subcutaneous versus visceral fat). €€€. Radiation (like many x-rays).

Bioelectrical impedance

Resistance between 2 electrodes is higher in obese individuals. Resistance high for fat & low for water. Not accurate.



Indirect methods for assessing fat mass

- Skinfold measurements – subcutaneous fat measured using calipers. Use conversion tables to estimate body fat % to about 3-5% accuracy. More useful than BMI in athletes.

Source: hereandnowwellness.com

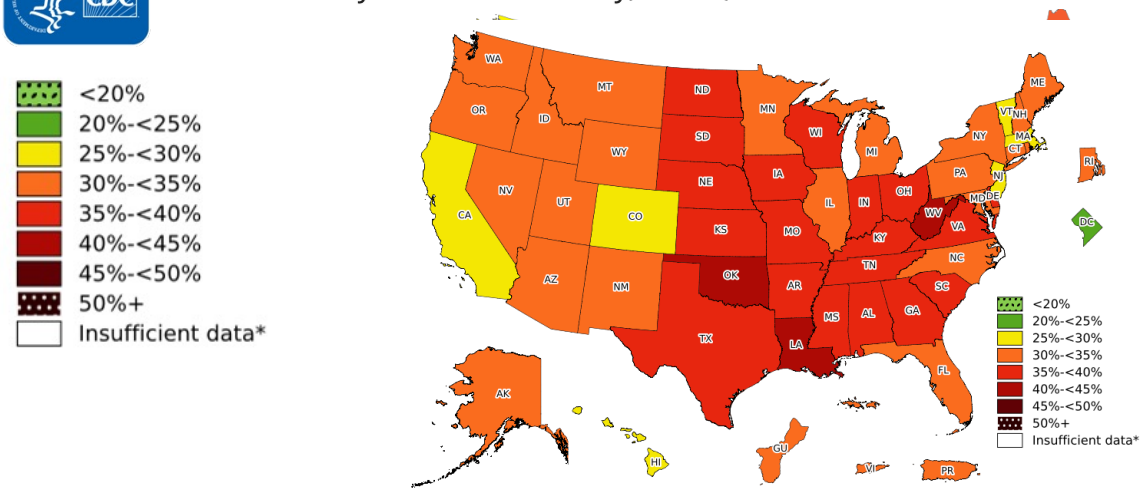
- Waist:hip ratio – cut-offs are ≥ 0.90 cm in men and ≥ 0.85 cm in women

- BMI - based on weight and height (kg/m^2)

Most obesity statistics are based on BMI data

2020: % US adults with an obese BMI (>30)

Prevalence† of Obesity Based on Self-Reported Weight and Height Among U.S. Adults by State and Territory, BRFSS, 2022



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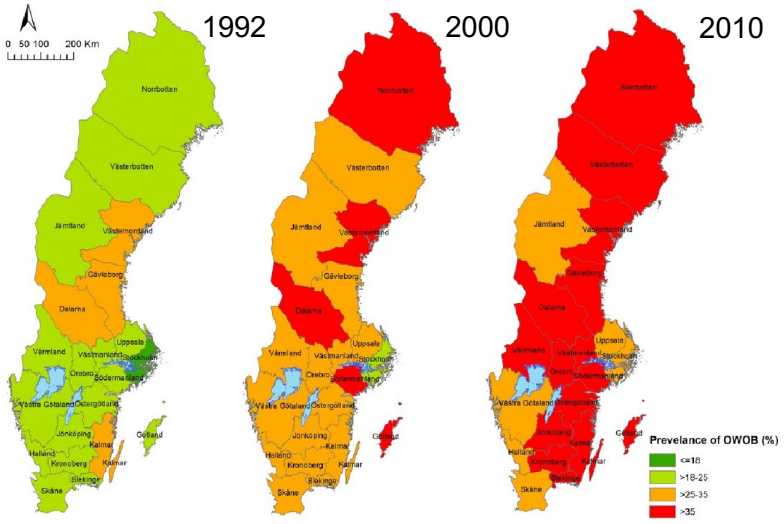

Sweden – Prevalence of Overweight (%)

% BMI>25 kg/m^2

- <18
- >18-25
- >25-35
- >35

And in 2022
Adults – 35% overweight, 16% obese
Children – 20% overweight.

DOI:10.1177/1403494815579478

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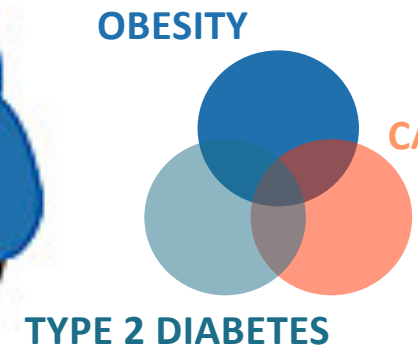
Health consequences of obesity



Increased risk:
Breast cancer
Bowel cancer
Osteoporosis
Lung disease
Strokes
Heart attacks

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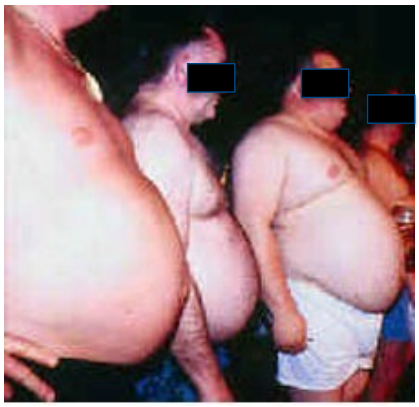
Metabolic Syndrome



A cluster of conditions that occur together, increasing risk of heart disease, stroke and type 2 diabetes.

About two-thirds of people suffering from obesity develop metabolic syndrome.

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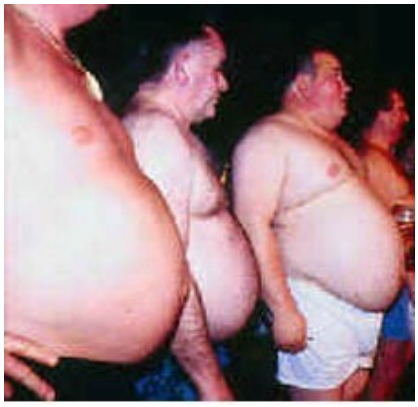
Metabolic Syndrome Diagnosis (WHO 1998)



Type 2 diabetes plus 2 out of 3 of the other components:

Type 2 diabetes:
- ↑ Fasting glucose (> 6.5 mmol/L)
- ↓ *Glucose tolerance* or
- ↑ Insulin resistance

Blood fat disturbance:
- ↑ Triglycerides
- ↓ *HDL (good) cholesterol*
- ↑ LDL (bad cholesterol)

High Blood Pressure

Visceral Obesity

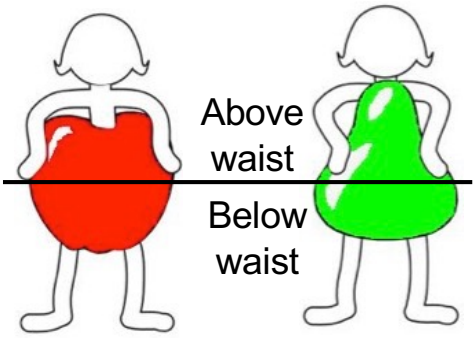
Debate regarding metabolic syndrome

We say that "it is just a constellation of symptoms or sub-diseases"

Depositphotos

We disagree. Surely there is a causal relation between symptoms – perhaps even a common cause?

- Android
- Central
- Abdominal
- Truncal
- Upper body

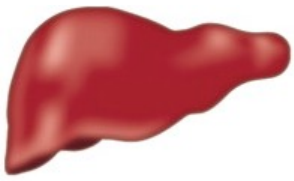


- Gynoid
- Peripheral
- Gluteo-femoral
- Lower body

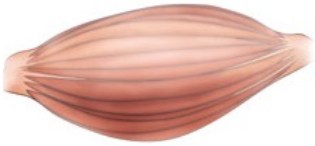
Increased risk of metabolic disturbances
↑ Visceral fat → ↑ Free Fatty Acid (FFA) release , e.g. to the liver (bad)
→ ↑ release of **adipokines*** (exception is adiponectin, whose secretion is decreased).

***Adipokines** are fat-derived cytokines such as leptin and resistin and also immune-stimulating hormones e.g. interleukin-6 (IL-6), TNFα

How does obesity cause insulin resistance?

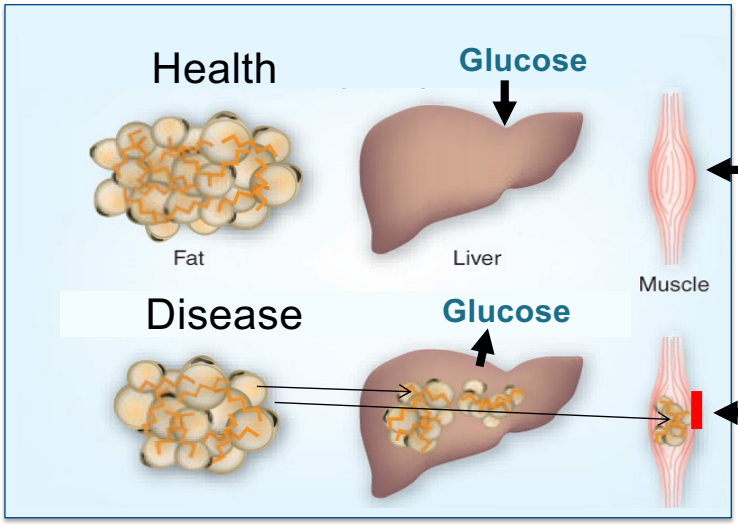


1. Free fatty acid ”overflow hypothesis”
2. Adipokines, immune stimulating hormones from white adipose tissue (↑ TNFα, ↑ resistin, ↓adiponectin)



Both can be true!

1. Fat overflow hypothesis. Fat outside fat tissue is dangerous for metabolic health



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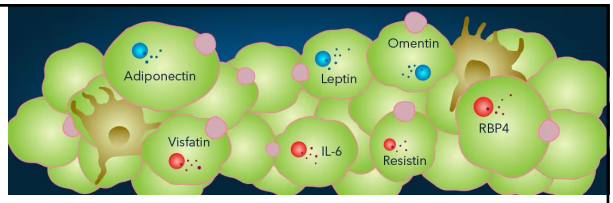
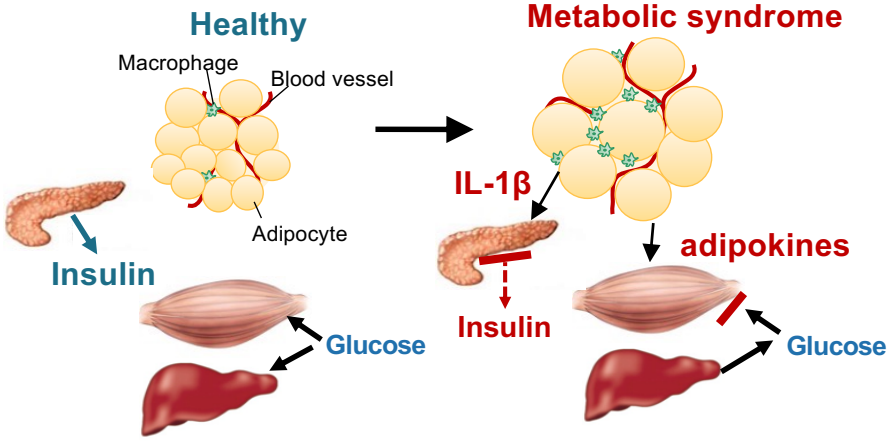
2. "Adipokine" hypothesis





Immune stimulating hormones (adipokines) from adipocytes and macrophages in fat → inflammation→ diabetes in liver, muscle and pancreas

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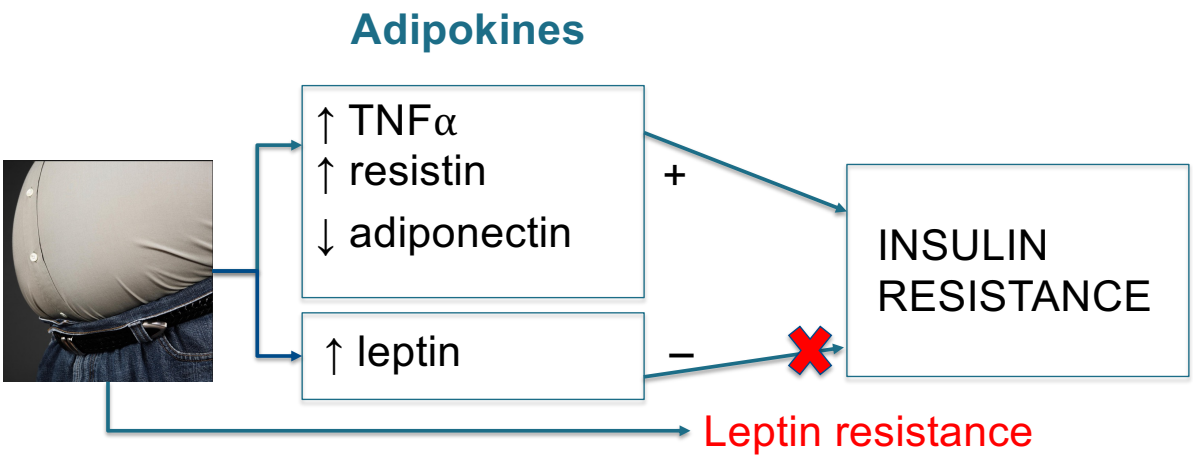
The relation between obesity, adipokines and their impact on insulin resistance



Adipokines in metabolic syndrome

Adipokines include proteins that:

1. modify insulin sensitivity e.g. acylation stimulating protein, tumor necrosis factor α (**TNF-α**), **IL-6**, resistin, visfatin, apelin, omentin, chemerin, leptin and **adiponectin**.

2. ↓ insulin release (e.g. IL-1β)

3. impact on vascularity e.g. angiotensinogen, plasminogen inhibitor protein, PAI-1) among others.

Adiponectin – Levels **reduced** in metabolic syndrome. In normal weight individuals, it has beneficial effects (increases insulin sensitivity, anti-inflammatory, anti-artherosclerosis).

TNFα & IL6 - Levels increased in metabolic syndrome. Proinflammatory. Produced by adipocytes and macrophages. Cause insulin resistance and increase circulating free fatty acids.

Adipokines in metabolic syndrome

I'm not expecting you to memorize this list but to realise they have many & diverse functions

Role in many metabolic processes:

Energy expenditure, neuroendocrine function, immune function, vascular remodelling, angiogenesis, fatty acid oxidation, lipogenesis, gluconeogenesis, glucose uptake, insulin signalling, and energy expenditure in metabolically active tissues such as the liver, skeletal muscle and the brain.

Site of action:

Can act locally, through autocrine/paracrine mechanisms, or systemically, through endocrine effects

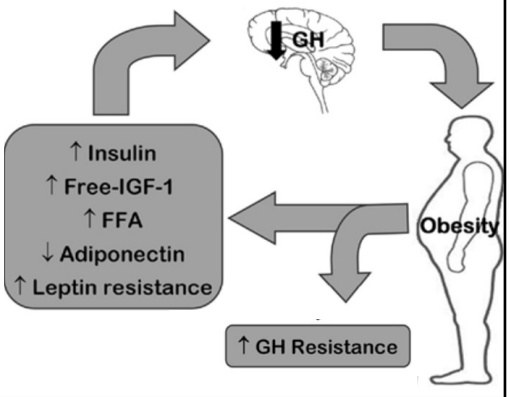
Additional endocrine changes in metabolic syndrome

↔ Cortisol (despite signs of ↑ cortisol activity - **looks like Cushings syndrome!**)

↑ androgens in women (polycystic ovarian syndrome, PCOS)

↓ androgens in men

↓ growth hormone



Body weight homeostasis

- Powerful physiological processes aim to keep body weight constant

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"Set point" hypothesis of body weight regulation

Food intake & energy expenditure balanced → body weight maintained at a "set point".

Energy Expenditure:
- Basal Metabolism
- Physical activity
- Adaptive thermogenesis**

Factors influencing the "set point"

1. **Genetic predisposition***
2. **Long term changes in body weight**
3. **Obesogenic environment**

- Target weight maintained with an extraordinary degree of control.
- "Set point" controller = brain (especially hypothalamus)

*Predisposition= tendency to suffer from
**Occurs in brown adipose tissue.

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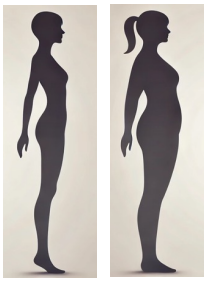
"Set point" is a hypothesis to explain obesity!!!

In obesity, there is a **defense of an elevated body weight**, rather than the absence of regulation.

Evidence that we defend our body weight at a set point?

- Body weight defended despite diet attempts (↑ hunger & ↓ metabolism).
- Diet and lifestyle changes ineffective.
- Return to "set point" (normal weight) after dieting or illness and after voluntary overfeeding.
- The 0.5 kg gained per year during ageing (average) = surprisingly little



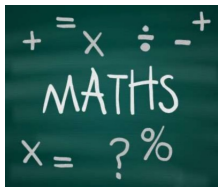
Age: 20 50

+ 30 kg

Weight gain as we age

Age 20 Age 50

+ 15 kg



1 g fat = 9 kcal
15 kg fat = 130,000 kcal
13,000 kcal in 30 years
= 86 kcal/week

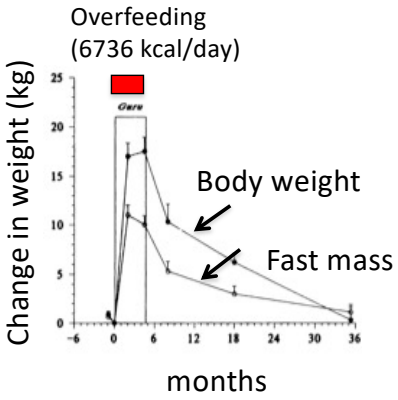
Per week imbalance:

or

8 minutes running

Powerful Physiological Systems Control Energy Balance & Body Weight.

Evidence for set point: Return to normal weight after a period of voluntary over-feeding



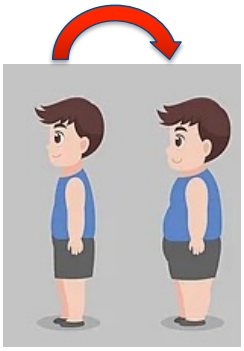
"Guru Walla" fattening session in the Massas ethnic group in Northern Cameroon

*"The fattening session resulted in a mean extra energy intake of 955 MJ and an increase of 17kg in body weight...**Over the whole overfeeding session, we noted a 43.5% mean increase of resting metabolic rate, which is much higher than previously reported"***

Pasquet P, Apfelbaum, M. Am J of Clin Nut 1994;60:861-3

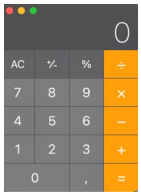
Does energy expenditure adjust if we over- or under-eat enough calories to alter our body weight?

Over-eat → gain 10% body weight



Measure Energy Expenditure

Predict Energy Expenditure



Difference??

Diet → Lose 10% or 20% body weight

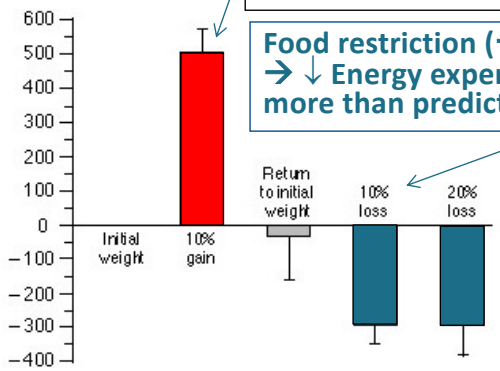
Leibel RL et al. N Engl J Med 1995;332:621-628.

Does energy expenditure adjust if we over- or under-eat enough calories to alter our body weight?

Over-eating (→ weight gain)
→ ↑ Energy expenditure (> 500 kcal above that predicted)

Food restriction (→ weight loss)
→ ↓ Energy expenditure (↓ was > 300 kcal more than predicted)

Observed minus predicted total energy expenditure (kcal)

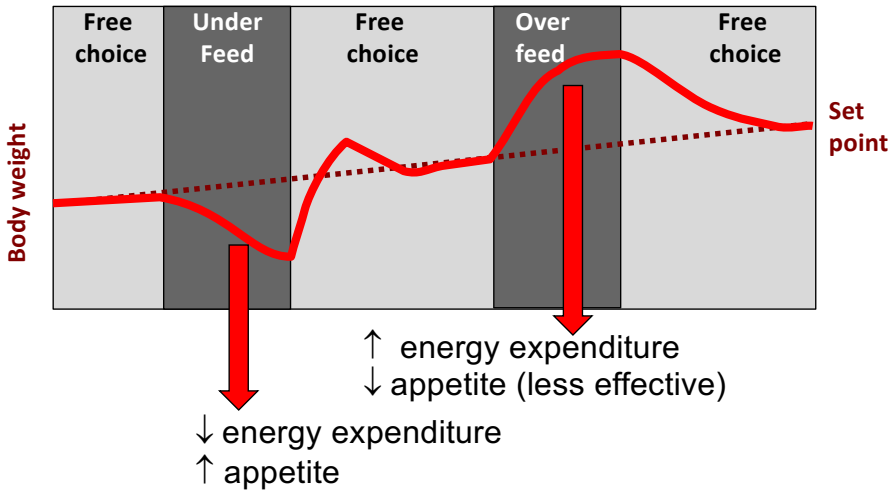


Dieter's curse

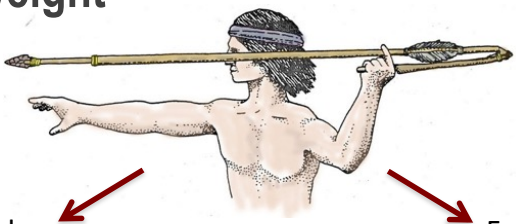
People go up in energy expenditure when they gain weight & down in energy expenditure when they lose it – more than expected!

Leibel RL et al. N Engl J Med 1995;332:621-628.

Both under- and over-nutrition can lead to weight gain over time



THEN….. In our evolution, there was genetic pressure to increase body weight



LEAN ENVIRONMENT

Food available

EAT!!!!
STORE ENERGY
(TO PREPARE FOR FUTURE FAMINE)

Food scarce (famine)

↑↑ HUNGER → search for food
↓ METABOLISM → save energy

survival

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NOW: Food is more available … but our genetics have evolved to increase our body weight

Same genetic pressures as our ancestors

OBESOGENIC ENVIRONMENT

Food available 24/7

Dieting (attempts to limit weight gain)

EAT!!!!
STORE ENERGY
(TO PREPARE FOR FUTURE FAMINE)

↑↑ HUNGER → search for food
↓ METABOLISM → save energy

Obesity

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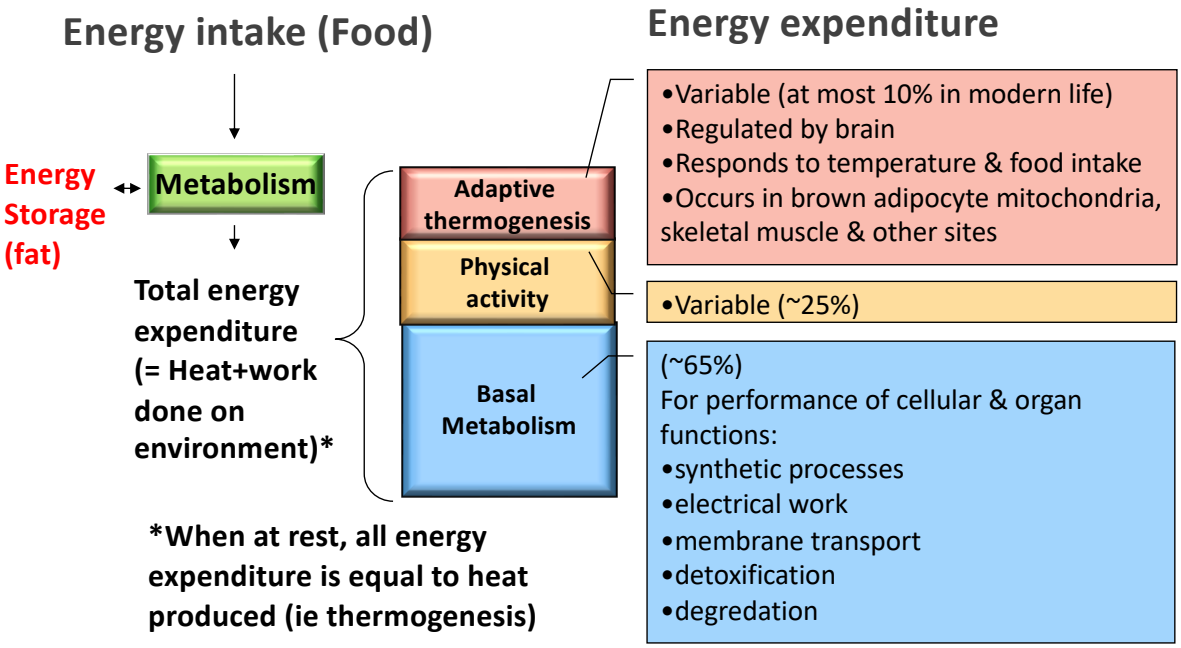

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Adaptive thermogenesis

Energy dissipated (wasted) in the form of heat in response to environmental changes, essentially **cold exposure** and **food intake**. It helps protect against weight gain by causing a compensatory increase in energy expenditure when we eat.

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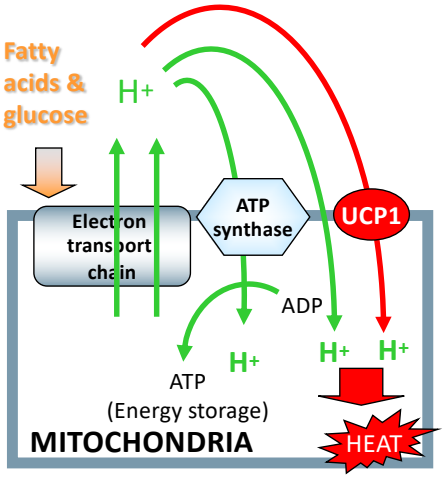
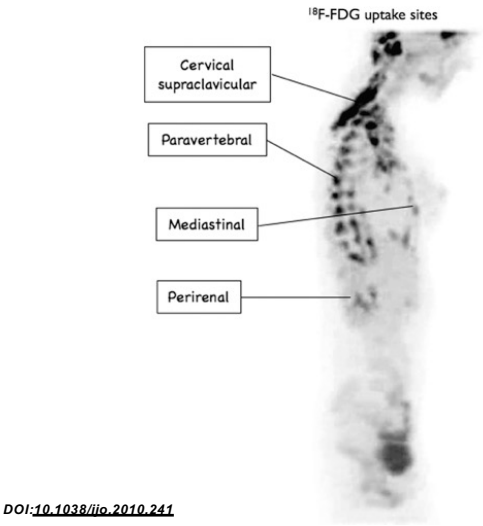
Brown Adipose Tissue (BAT)

- Function = **energy expenditure** (not storage).
- Present in interscapular area. Present in human infants but declines with age.
- Sympathetic nervous system (SNS) increases BAT activity in response to cold or increased food ingestion. **Adaptive thermogenesis.**
- Heat generated in mitochondria via "uncoupling".



UCP1=uncoupling protein 1
It is present in BAT but not in other cells. It is increased by over-eating and decreases with fasting

2010: BAT also discovered to be present in human adults



DOI:10.1038/ijo.2010.241

PET scan after intravenous injection of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) → BAT visualized

New information on BAT:
Present in human adults.
Women have more than men.
More in younger adults
More BAT in lean subjects?

Therapeutic interest?
Stimulation of BAT → energy expenditure & weight loss

Hormones important for BAT activation

1. Noradrenaline (β3 AR on BAT) – acute

Caused by sympathetic nervous system (SNS) activation. Contribute to heat produced when emotionally stressed.

↑ Metabolism of brown adipose tissue (BAT).

↑ UCP1 activation and hence energy expenditure

2. Thyroid hormones (TRβ on BAT) - chronic

↑ UCP-1 expression in BAT

(BUT NOTE: THEY ARE ALSO THE PRIMARY CONTROLLER OF THE BASAL METABOLIC RATE; ACTING ON MOST BODY CELLS (NOT BRAIN) TO ↑↑ ENEGY EXPENDITURE)

3. Glucocorticoids (via glucocorticoid receptor on BAT)

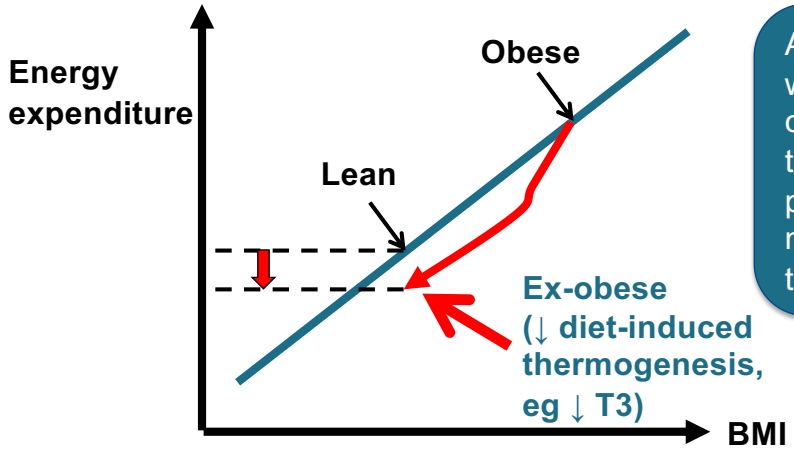
Inhibitory effect on BAT.

Suppresses noradrenaline-induced UCP1 activation

4. Leptin (via ObRB in hypothalamus that stimulate SNS)

↑ UCP-1 expression in BAT

Reduced energy expenditure in the post-obese state



A formerly obese individual will require ~300–400 fewer calories per day to maintain the same body weight and physical activity level as a never-obese individual of the same body weight.

Body weight Homeostasis - the control systems

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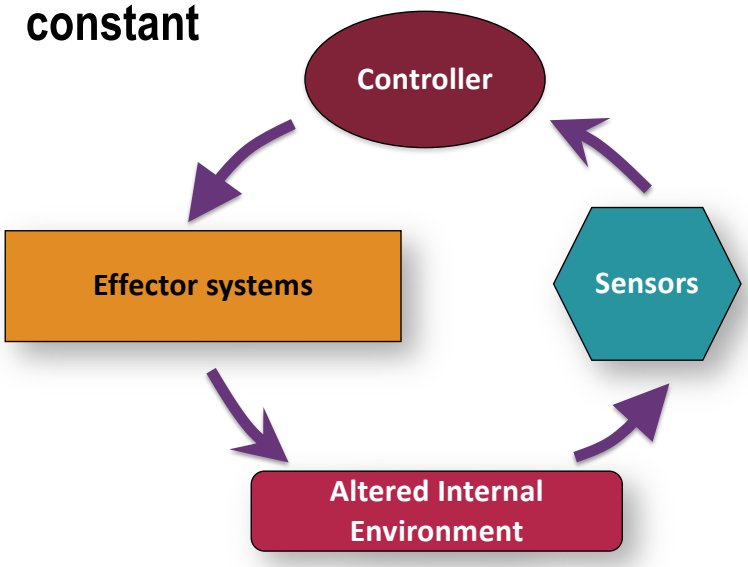
Principles of homeostasis – keeping (body weight) constant



Homeostasis
- maintaining a steady state.
- involved feedback systems.

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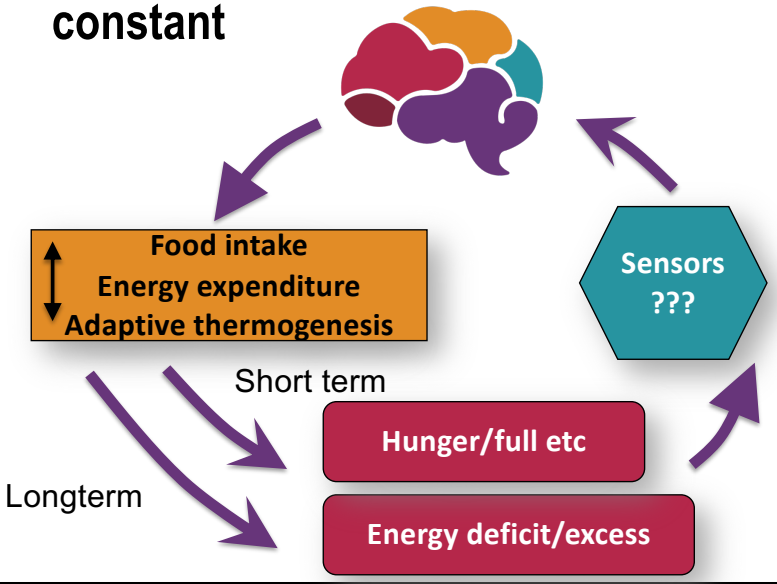
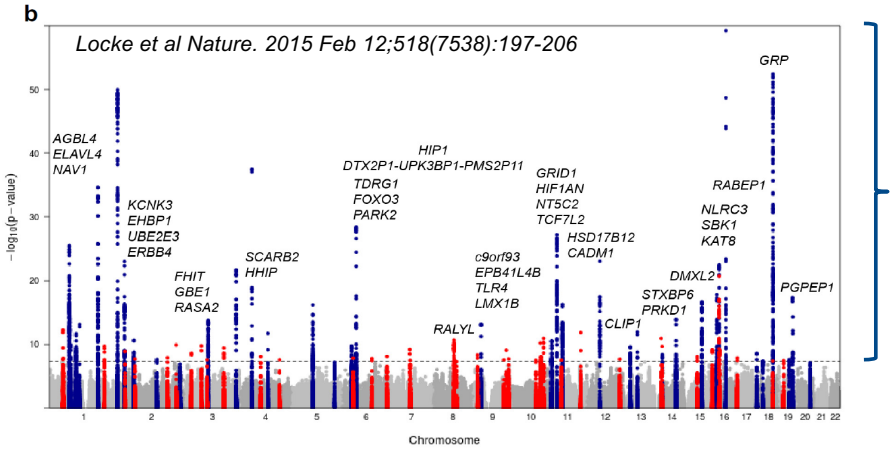
Principles of homeostasis – keeping (body weight) constant



Key questions:

1. What are the control systems in the brain that alter food intake & energy expenditure?
2. What are the sensors?
3. Why do these fail in ways that result in body weight gain & obesity?

Energy homeostasis control system is in brain

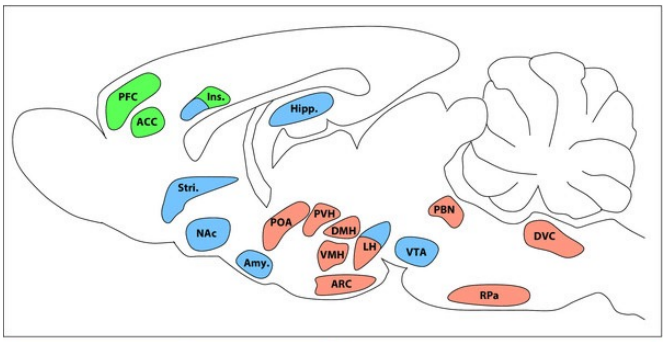


Common variants at only two loci, *FTO* and *MC4R*, have been reproducibly associated with body mass index (BMI) in humans. To identify additional loci, we conducted meta-analysis of 15 genome-wide association studies for BMI ($n > 32,000$) and followed up top signals in 14 additional cohorts ($n > 59,000$). We strongly confirm *FTO* and *MC4R* and identify six additional loci ($P < 5 \times 10^{-8}$): *TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2* and *NEGR1* (where a 45-kb deletion polymorphism is a candidate causal variant). Several of the likely causal genes are highly expressed or known to act in the central nervous system (CNS), emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity.

NATURE GENETICS VOLUME 41 | NUMBER 1 | JANUARY 2009 25

Genes linked to BMI are mostly found in brain, and notably in the hypothalamus

Brain areas involved in energy balance regulation



Autonomic	Executive	Reward
Sensing of nutritional or energy reserve status (homeostatic signals) Relaying homeostatic signals to the forebrain Controlling adaptive thermogenesis	Decision to eat (and to commit to exercise)	Establishing the hedonic ("liking") and incentive or motivational salience ("wanting") properties of eating-related stimuli

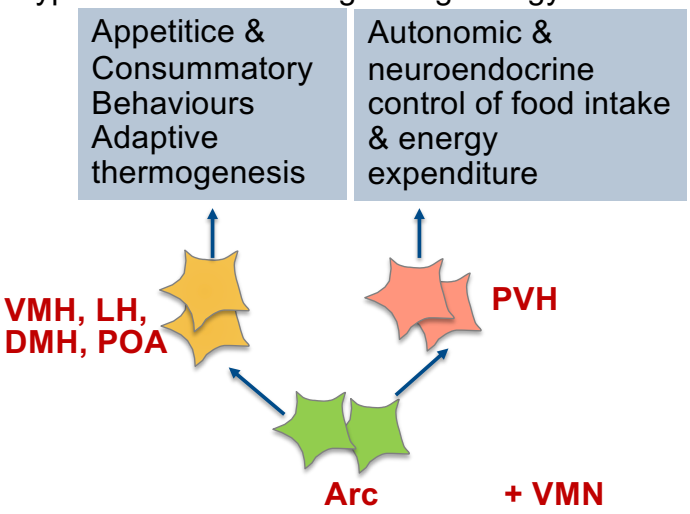
DOI:10.1111/nyas.13263

Hypothalamic and **brainstem** autonomic circuitry (orange) includes the arcuate nucleus (ARC), the dorsomedial hypothalamus (DMH), the dorsal-vagal complex (DVC), the lateral hypothalamus (LH), the pontine parabrachial nucleus (PBN), the preoptic area (POA), the paraventricular hypothalamus (PVH), the raphe pallidus (RPa), and the ventromedial hypothalamus (VMH). Structures of the brain **executive system** (green) include the anterior cingulate cortex (ACC), the insula (Ins.), and the prefrontal cortex (PFC). Structures of the **brain reward system** (blue) include the amygdala (Amy.), hippocampus (Hipp.), Ins., LH, nucleus accumbens (NAc), striatum (Stri.), and ventral tegmental area (VTA).

Autonomic control of energy balance: Hypothalamus

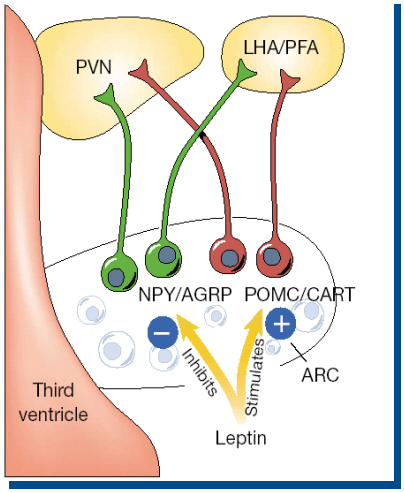
- Nearly all hypothalamic nuclei engaged.
- Especially - Mediobasal hypothalamus (**MBH**) - includes arcuate nucleus (**Arc**) and ventromedial nucleus (**VMN**) – energy intake and adaptive thermogenesis.
- Arc cells project to many other hypothalamic (and extra-hypothalamic) areas to regulate energy balance.
- Lateral hypothalamus – feeding center.

Hypothalamic areas regulating energy balance.



Johan's hypothalamic lecture – some key points

1. Lesions of key hypothalamic areas cause animals to lose control of their set point for body weight.
   - **Ventromedial nucleus (VMN)** lesion → obesity.
     Role = satiety center
   - **Lateral Hypothalamus (LH)** lesion → appetite loss.
     Role= hunger center
2. **Arcuate nucleus (Arc):** Contains orexigenic **AgRP/NPY** neurones and anorexigenic **POMC** neurones.
3. **Leptin** Fat-derived hormone that suppresses food intake. Activates POMC & inhibits AgRP/NPY neurones. Informs brain on fat stores. Leptin resistance in obesity.
4. Leptin and leptin receptor gene mutations – extremely rare monogenic cause of obesity.



Adapted from M.W. Schwartz

Autonomic control of energy balance: Brainstem

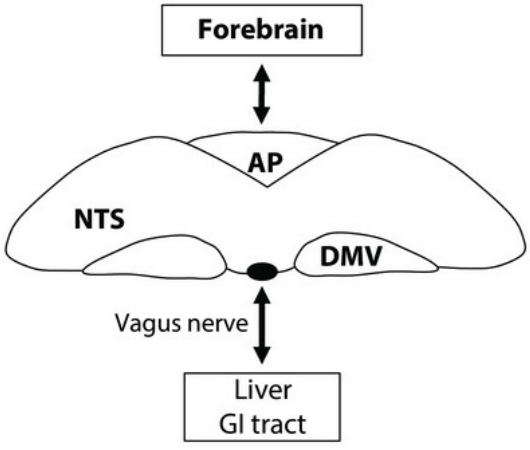
1. Dorsal vagal complex (DVC)

- nucleus of the solitary tract (**NTS**),
- area postrema (**AP**)
- dorsal motor nucleus of the vagus nerve (**DMV**)

Integrate homeostatic signals about nutritional and energy reserve status.

Involved in appetite suppression, malaise, response to infections, gut-brain signals, gastric distension, swallowing etc.

Important target for the anorexigenic peptide, GLP-1 (see later)



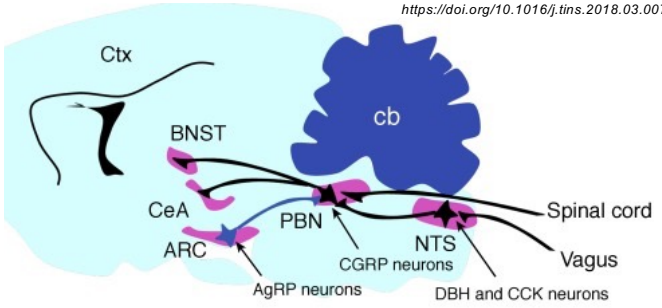
DOI:10.1111/nyas.13263

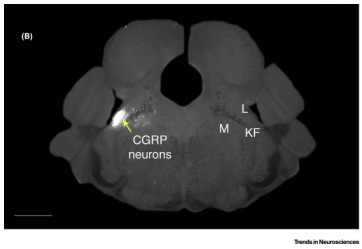
Autonomic control of energy balance: Brainstem

2.Parabrachial nucleus (an anorexic hub)

- Relays sensory information to forebrain.
- CGRP neurons relay aversive signals (e.g., food poisoning, pain, itch etc) to the amygdala (CeA), the bed nucleus of the stria terminalis (BNST) and other brain regions.
- **Chronic activation of CGRP neurons can lead to severe anorexia and starvation.**
- When activated, CGRP neurones block incoming orexigenic information from AgRP neurones in Arc.
- Other PBN neurons transmit taste, temperature, respiratory, satiety, thirst, salt-appetite, or glucose counter-regulatory signals.

https://doi.org/10.1016/j.tins.2018.03.007





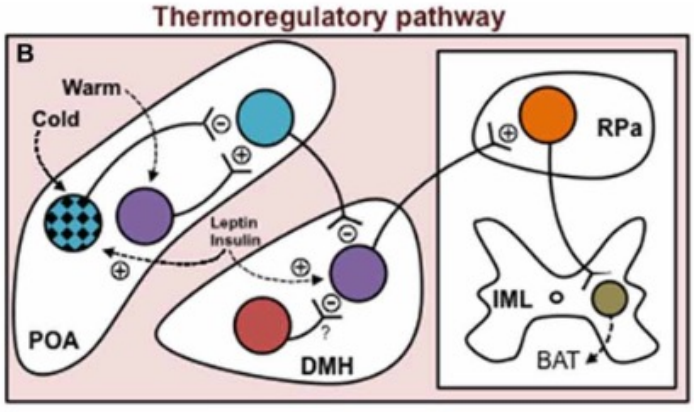
CGRP = calcitonin gene-related peptide

Anorexigenic

Autonomic control of energy balance: Brainstem

3. Others

The Raphe Pallidus (RPA) receives thermoregulatory information from the hypothalamus and projects to the intermediolateral nucleus (IML) of the spinal cord, from which originate the preganglionic neurons of the sympathetic nervous system (**SNS**) outflow **to BAT**.



DOI:10.1111/nyas.13263

POA (Preoptic area), DMH (Dorsomedial hypothalamus)

Role of the reward system

Motivation for food, including palatable foods.

Pleasure from food and food choice

Important when hungry (to help restore energy balance) but also to ensure we eat in excess of metabolic requirement (to help prepare for a future famine).

Golocalprov.com

Food reward – eating for survival (adaptation)

- **Sustaining energy** – eat when available, ↑ energy store for future need
- **Nutrition** – variety
- **Food selection/preference** – sweet, salty, umami >> sour, bitter (edible >> poisonous)

Food reward – eating against survival (maladaptation)

Vitagazette.com

News.bbc.co.uk

Food reward – eating for survival

"Appetite comes with eating; the more one has, the more one would have".

- Certain foods make us want to eat more (=**reinforcement**)
- They promote eating in the absence of hunger or energy need (**= hedonic, non-homeostatic feeding**)

Hunger increases the reward value of foods

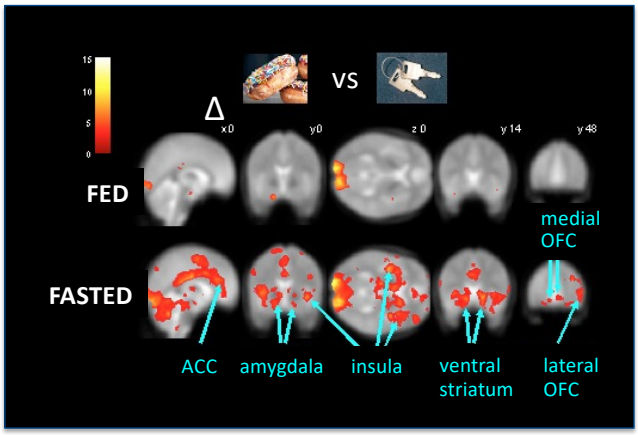


"Hunger is the best spice"
Swedish

"A good meal ought to begin with hunger".
French

Reward value also reflects:
Palatability, taste, orosensory experience, reward expectation/prediction, genetics

Brain areas linked to reward are more activated by photos of palatable foods when hungry than when fed

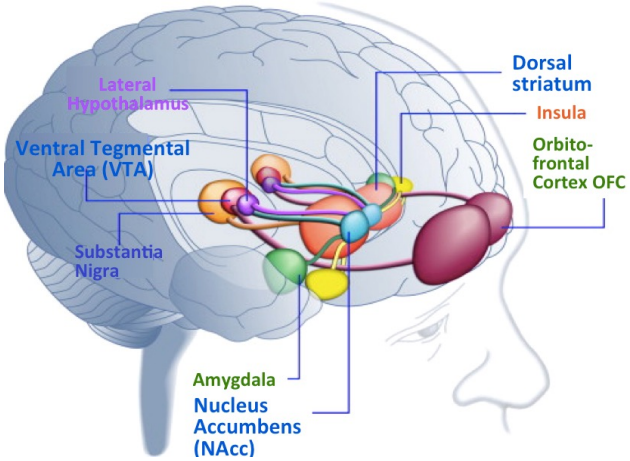


Goldstone et al., 2009, EJN

<u>Brain reward areas:</u>
- Activated by pictures of rewarding foods.
- Linked to food reward!
- Regulated by nutritional state.

→ **Brains pathways involved in (visual) food reward processing are regulated by metabolic signals**

Brain Areas Activated in Response to Palatable Food or Food Associated Cues



OFC & Amygdala → reward value of food

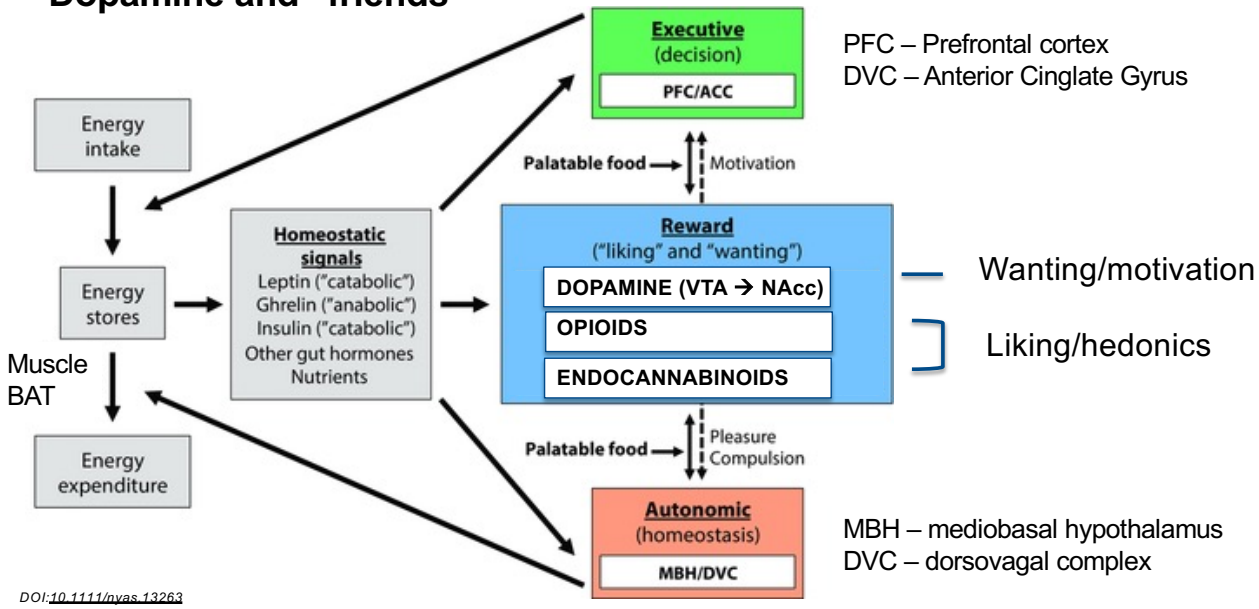
Insula → taste & hedonic evaluation

NAcc, VTA & dorsal striatum → Motivational and incentive properties of rewards

Lateral hypothalamus → regulates rewarding response to palatable food and drives reward-seeking behaviours

Adapted from Kenny PJ, 2010 Neuron 69: 664

Dopamine and "friends"

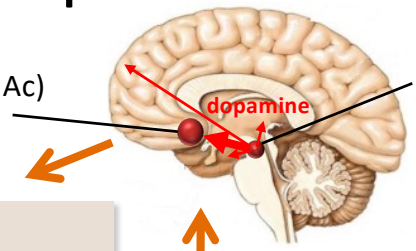


PFC – Prefrontal cortex
DVC – Anterior Cinglate Gyrus

MBH – mediobasal hypothalamus
DVC – dorsovagal complex

DOI:10.1111/nyas.13263

The midbrain dopamine neurones signalling reward



NAc
↑ dopamine release

VTA
↑ Cell firing

\+

Natural and artificial rewards

sex food gambling drugs alcohol

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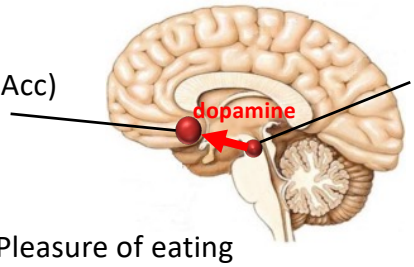
What does accumbal dopamine actually signal?




Golocalprov.com

- Pleasure of eating
  (Small et al, Neuroimage 2003)
- Novel (unexpected) rewards
  (Norgren et al, Physiol Behan, 2006)
- Reward anticipation (cue-induced eg smell)
  (Epstein et al, Psychol Rev, 2009)
- Motivational/incentive value
  (Volkow et al, Synapse, 2002)

Picturequotes.com

Increases "wanting" and approach behaviour for food

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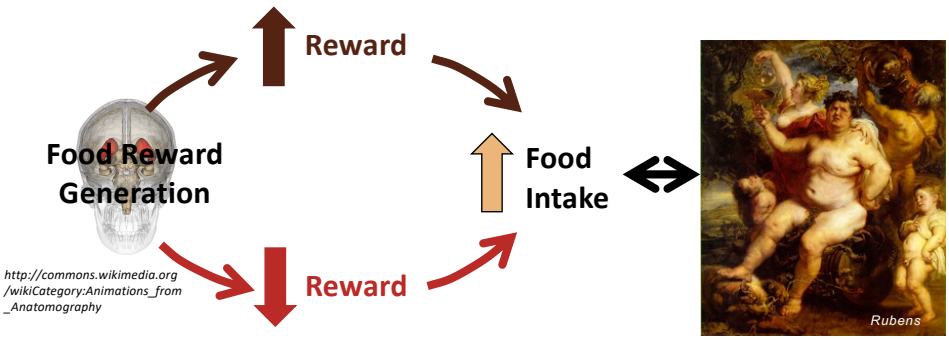
Obesity is associated with an altered reward function

"Gluttony" Hypothesis

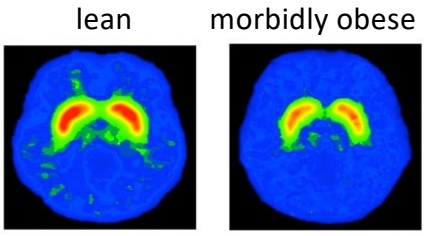


"Reward deficiency" Hypothesis

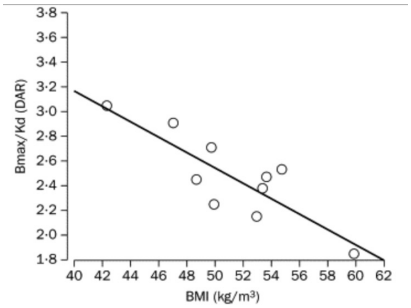
Evidence favours a reward deficiency hypothesis

Obesity is associated with an altered reward function

Volkow et al. 2008, Phil. Trans. R. Soc. B 363:3191



↓ Striatal dopamine D2 receptor availability in obese subjects.
(Similar to drug-addicted subjects).



… supports the **reward deficiency hypothesis** in obesity

Obesity is associated with an altered reward function

Potential "reward" contributors to obesity:

1. **Genetic** and other **pre-existing** differences in reward function

2. Changes in reward function that are **secondary effects of the obese state**.

3. Intake of palatable food as an **escalating, addictive process**

Could some obese patients be food addicted?

Could food be addictive?

Probably not a chemical-like addiction.

In man, there is no solid evidence that any food, ingredient, combination of ingredients or additive (exception = caffeine) causes us to become addicted to it!

More likely a behavioural addiction.

Certain obese individuals appear to express addiction-like behaviour to food eg binge eating disorder

http://www.neurofast.eu/consensus/

Tolerance

Dependence

Continued use despite known consequences

Preoccupation

Failed abstinence

Withdrawal

Many addiction criteria are difficult to apply to food and require severity or impairment thresholds

See Ziauddeen H et al., 2012, Nat Rev Neurosci

People that score high on the Yale Food Addiction Scale have a different brain response to food

Questionnaire → Food addiction score

fMRI brain imaging → Areas activated by anticipation & receipt of palatable food.

Correlations and comparisons

fMRI response in OFC

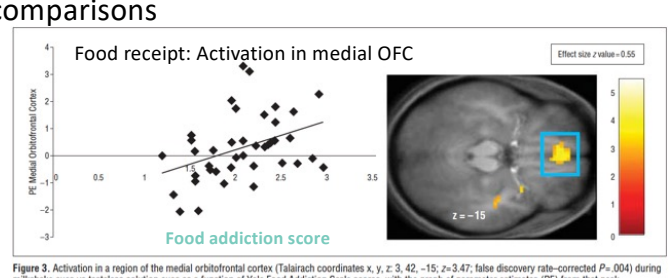


Figure 3. Activation in a region of the medial orbitofrontal cortex (Talairach coordinates x, y, z: 3, 42, −15; z = 3.47; false discovery rate–corrected P = .004) during milkshake cues vs tasteless solution cues as a function of Yale Food Addiction Scale scores, with the graph of parameter estimates (PE) from that peak.

"Food addicted" subjects - differing brain activity response – both for food anticipation and receipt.

Gearhardt AN et al., 2011, Arch Gen Psychiatry

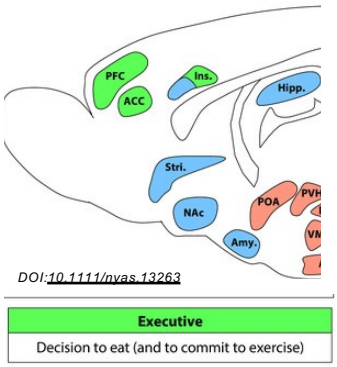
The cortical executive system and the decision to eat.

PFC circuits (incl. **ACC**) are close to and influenced by the adjacent olfactory, gustatory, and somatosensory cortices, which compose the **insula**.

Receive sensory information from the oral cavity and digestive tract.

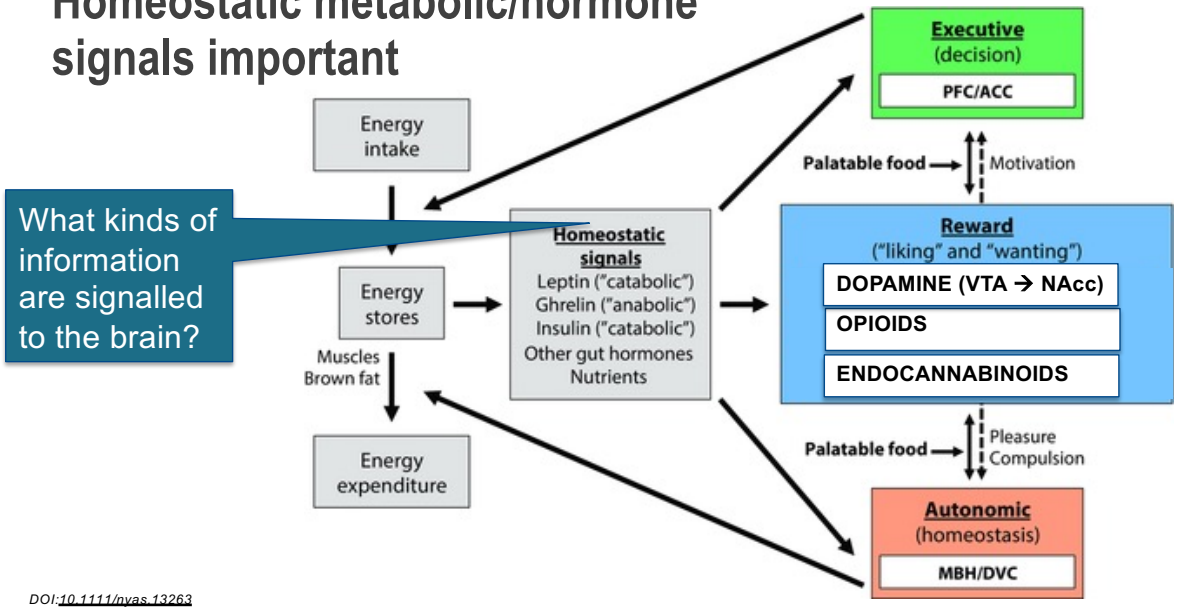
Play a decisive role in the eating; the ultimate decision of eating is conscious and voluntary.

This can over-ride homeostatic drives, for example.



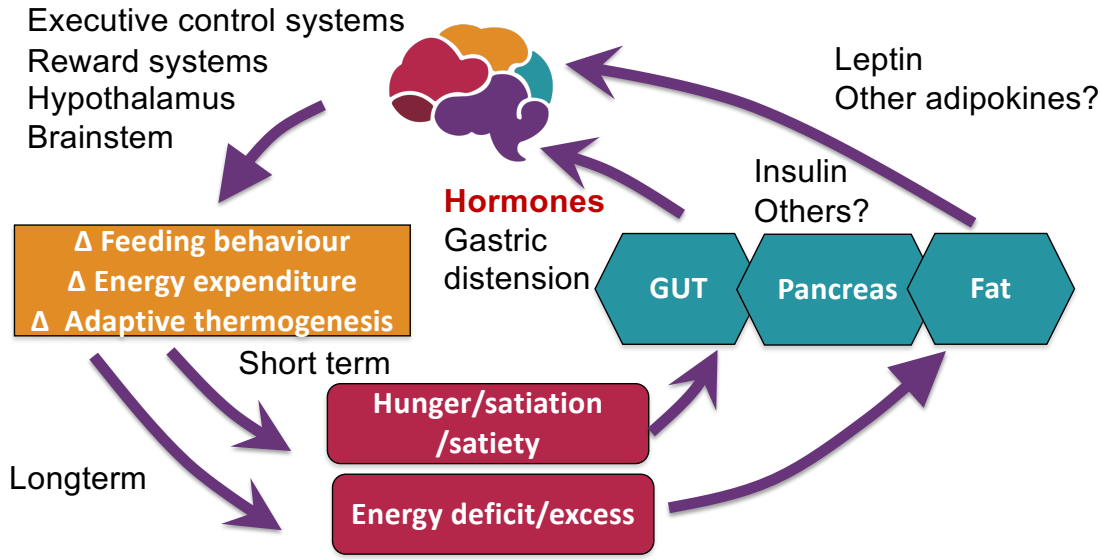
Pre-frontal cortex
Anterior cingulate cortex
Insula

Homeostatic metabolic/hormone signals important



DOI:10.1111/nyas.13263

Energy Homeostasis: filling in the gaps



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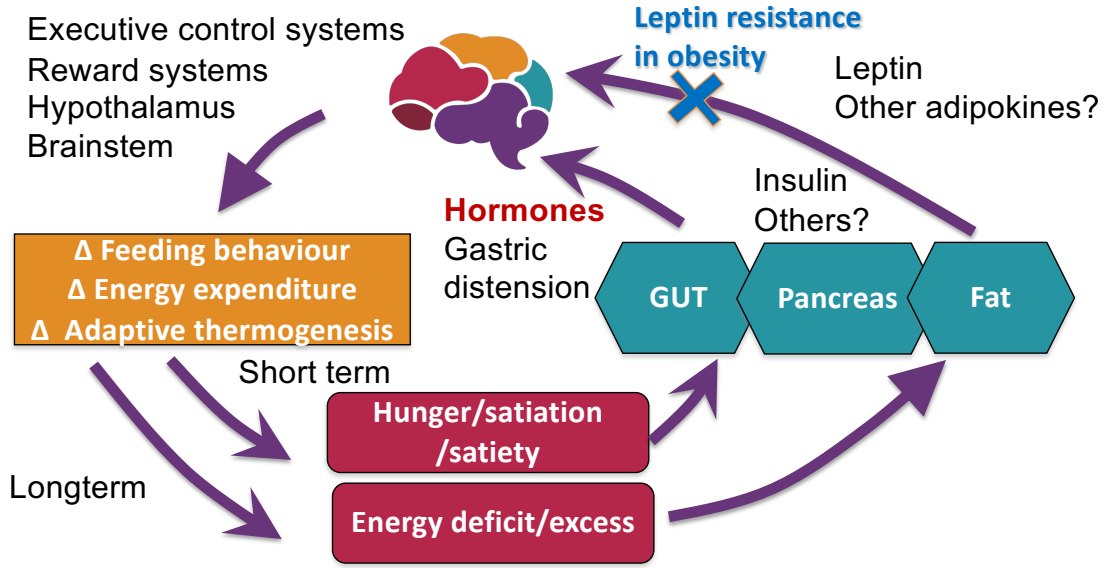
Energy Homeostasis: filling in the gaps



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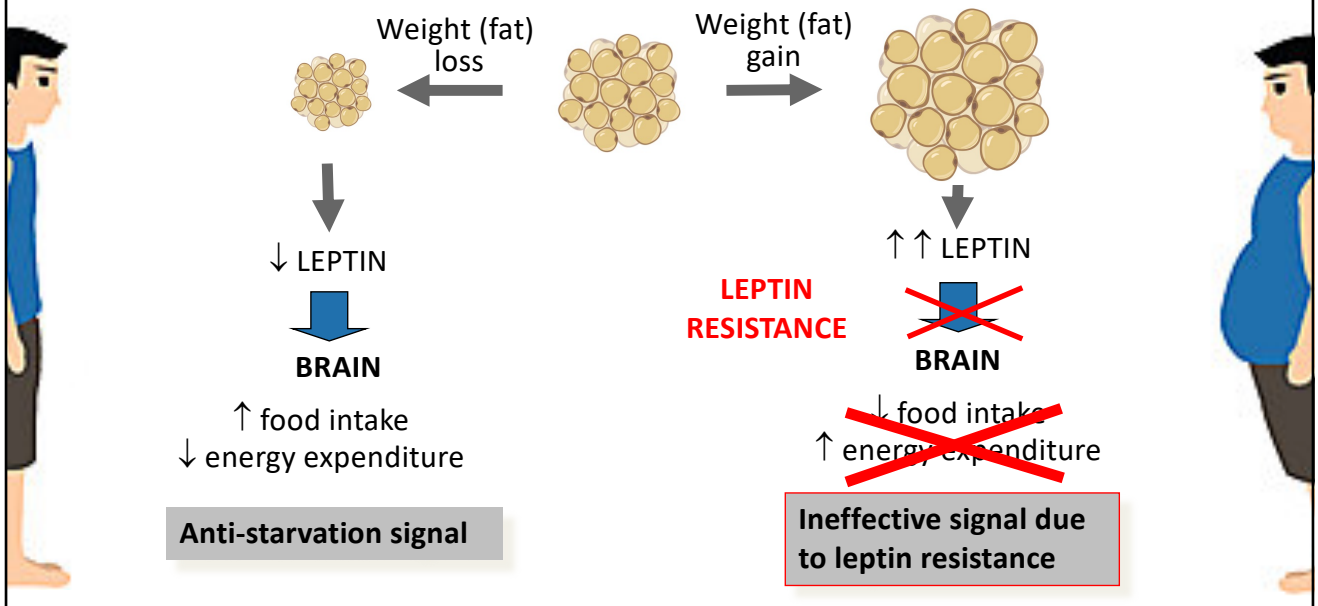
Leptin resistance in obesity – the brain no longer "hears" the signal



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Eating – for energy requirements & to have reserves

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The Brain's Energy Balance Systems: survival

… when food is scarce

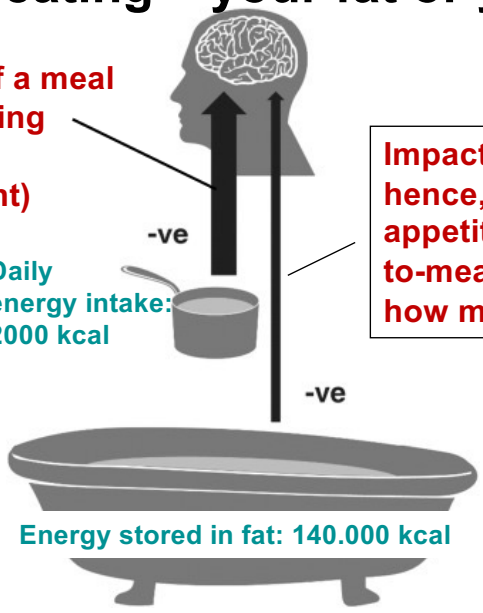
Reduce metabolism

Food searching & consumption

Who drives eating – your fat or your gut?

Impact of a meal on reducing appetite (important)

Signals & mechanisms ?

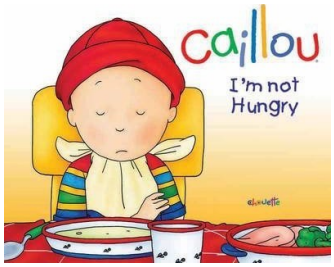


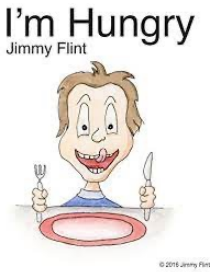
Impact of energy stores (and hence, leptin) on reducing appetite – cannot be the meal-to-meal determining factor on how much we eat.

DOI: 10.1016/j.physbeh.2016.03.038

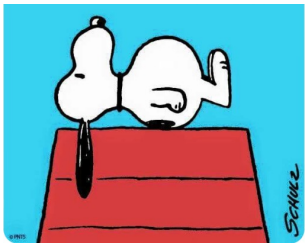
The meal cycle: hunger, satiety and satiation

I'm not hungry (=satiety)





I'm full (= satiated)



Hunger, Satiety & Satiation

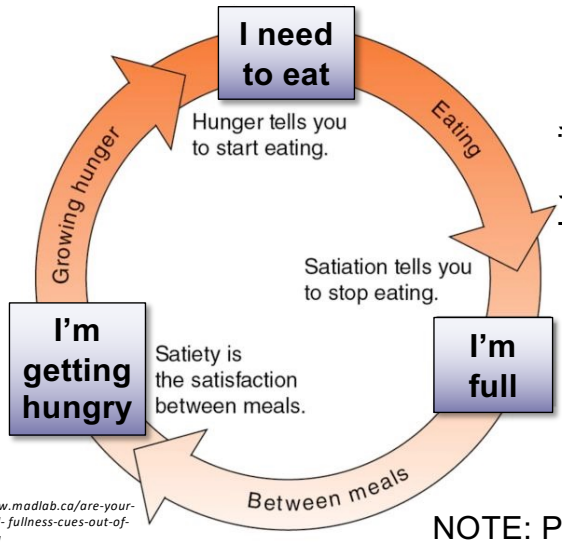
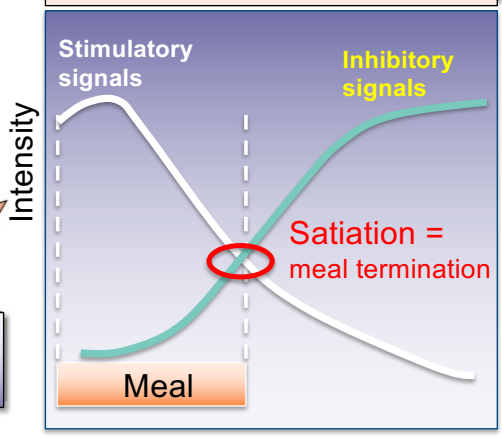


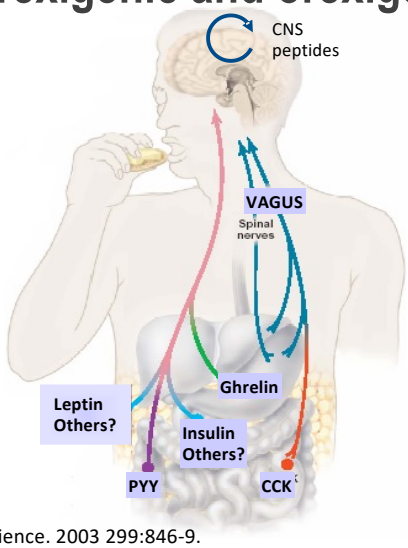
Image: https://www.madlab.ca/are-your-hunger-and-fullness-cues-out-of-whack.html

Satiety = absence of appetite/hunger until the next meal



NOTE: People commonly confuse satiety & satiation

Anorexigenic and orexigenic hormones



<u>Anorexigenic (i.e. eat less)</u>

A. Increase satiety,
B. Increase satiation,
C. Cause nausea or aversion,
D. For some hormones, their anorexigenic mechanism is unclear (ie. A,B and/or C)

<u>Orexigenic (i.e. eat more)</u>

E. Increase hunger

Marx J, Science. 2003 299:846-9.
Murphy K, Bloom SR. Nature 444, 854-859

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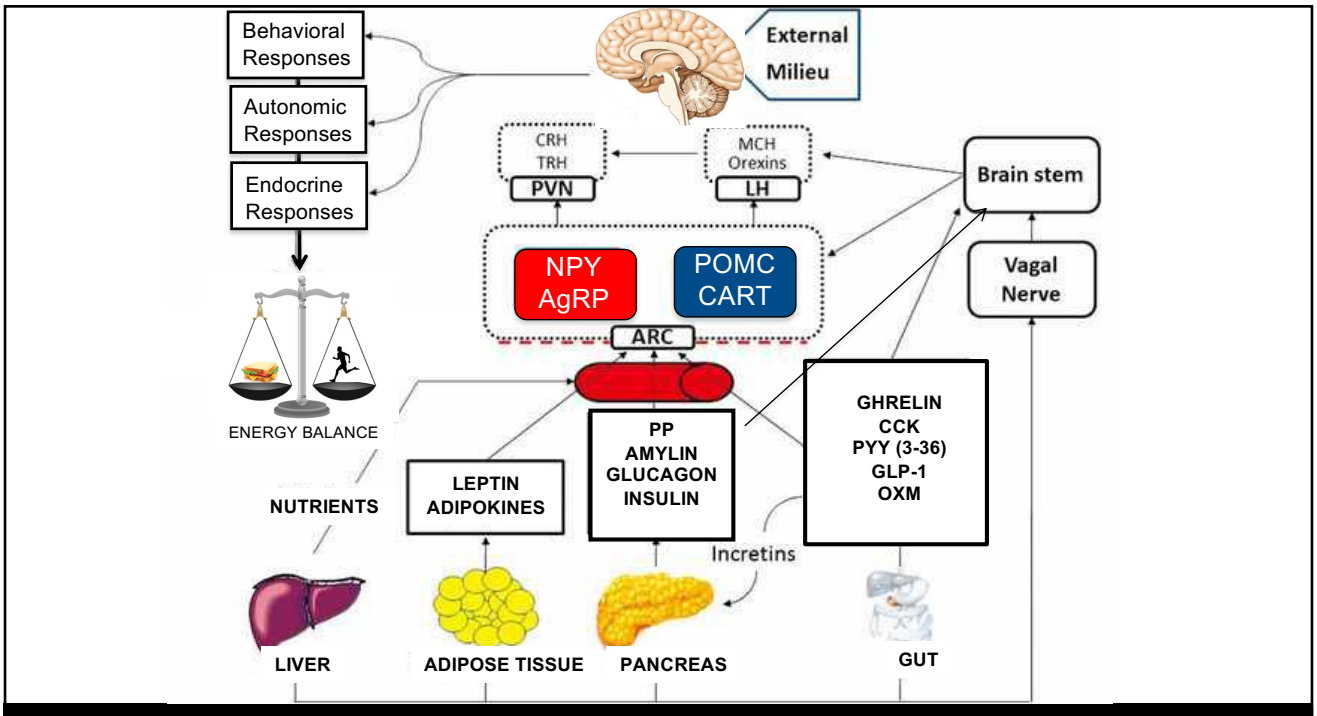

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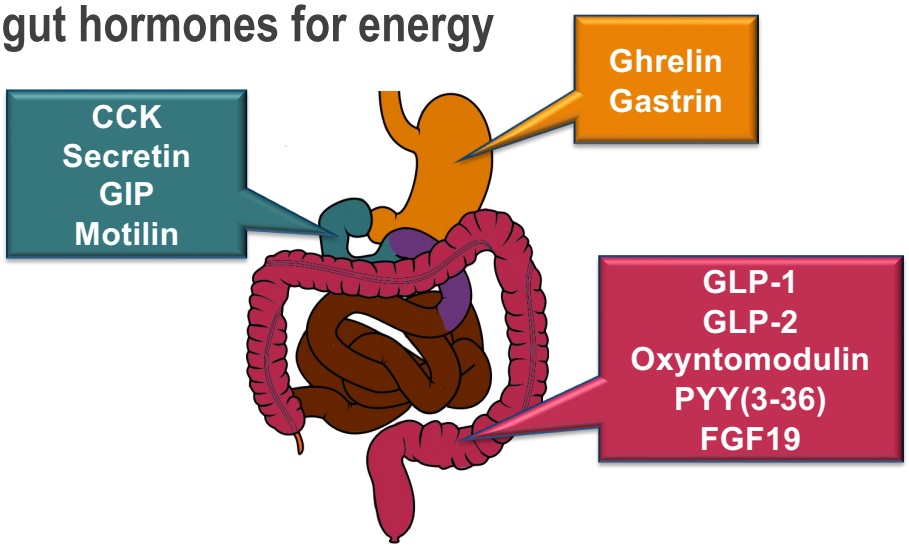
Important gut hormones for energy balance



GLP-1 and GLP-2 (Glucagon-like peptides), CCK (cholecystokinin), GIP (Gastric inhibitory peptide), Peptide YY 3-36 (PYY_{3-36}), Fibroblast growth factor 19 (FGF19)

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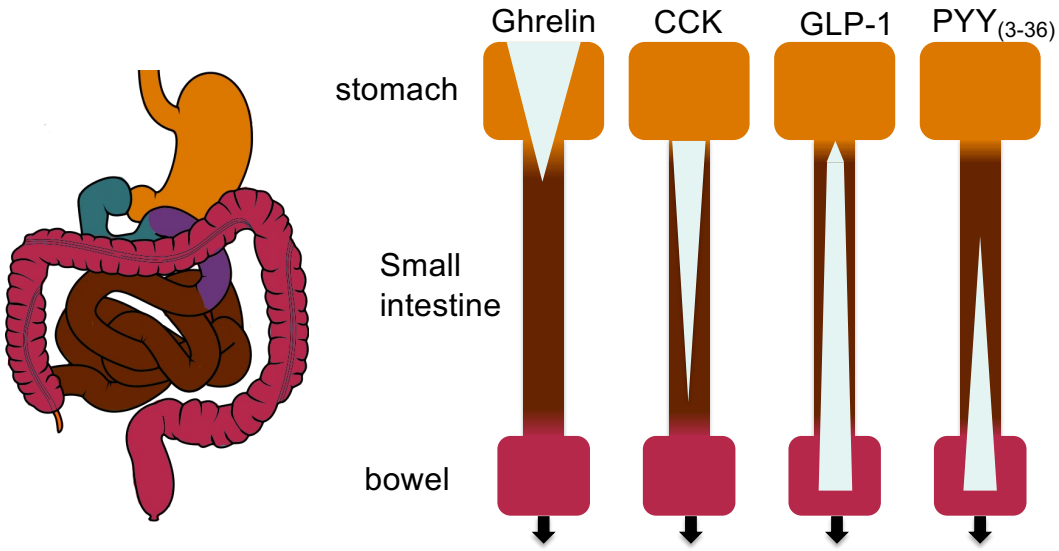
Distribution of enteroendocrine cells in gut



Steinert et al., Physiol Rev 2017; 97:411

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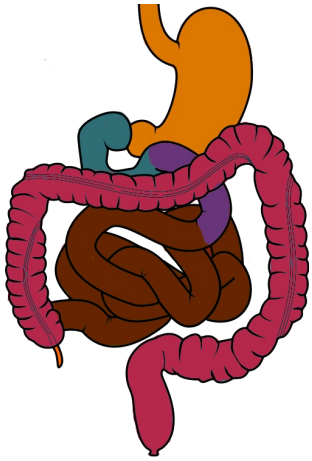

Cell type	Highest density	Peptide released
G-cells	Stomach	Gastrin
X-cells	Stomach	**Ghrelin**
ECL-cells	Stomach	Histamine
???	Stomach & duodenum	Gastrin-releasing peptide (GRP)
S-cells	Duodenum and jegunum	Secretin
I-cells	Duodenum and jegunum	Cholecystokinin **(CCK)**
K-cells	Duodenum and jegunum	Glucose-dependent insulinotropic peptide (**GIP**).
N-cells	Ileum	Neurotensin
L-cells	Ileum and Colon	Glucagon-like peptide **(GLP-1)**
L-cells	Ileum and Colon	**PYY3-36**
D-cells	Entire GI tract	Somatostatin
EC-cells	Entire GI tract	Serotonin

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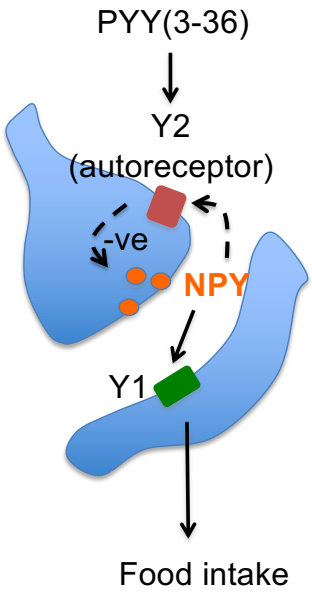
Gut peptides influencing energy balance
1. PYY (3-36):

- Anorexigenic. Produced esp. by the ileum, colon and rectum (**L cells**) in response to feeding/meals.
- Signals **satiety** (long inhibition of eating).
- **It is an agonist at the Y2 receptor (ie NPY receptor subtype 2), a presynaptic NPY receptor. (Note: other NPY receptors are post-synaptic). C.f. NPY acting at Y1 post-synaptic receptors that is orexigenic)**
- Target systems: **Arc very important** for anorexigenic effect. Y2 receptors also located in DVC and amygdala.
- Obesity does not appear to be associated with reduced PYY3-36 levels although there are promising effects to reduce meal size.



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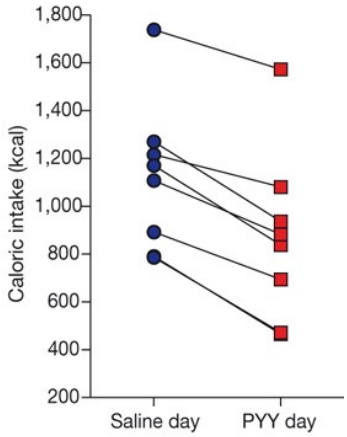
In healthy subjects, PYY(3-36) reduces caloric intake in a buffet meal



Batterham et al., *Nature* **450**, 106-109

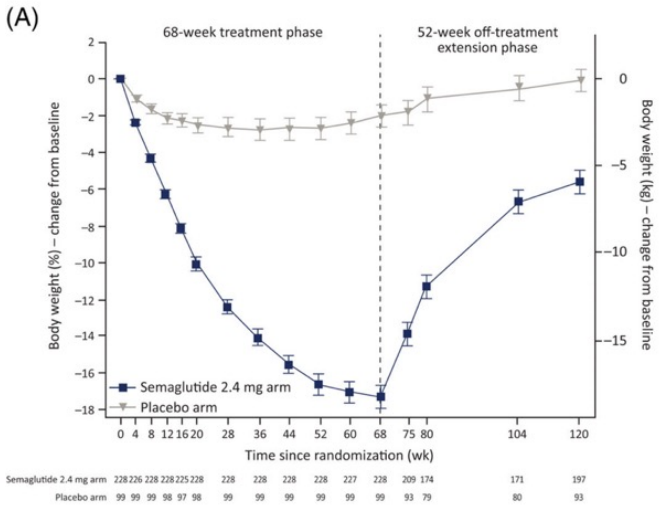
Gut peptides influencing energy balance
2. GLP-1 (and oxyntomodulin)

Gila monster lizard

- Mostly produced in the ileum, in the **L cells** (that also produce PYY_{3-36})
- Proglucagon (precursor for GLP-1, glucagon, glucagon-like peptide-2 (GLP-2) and oxyntomodulin).
- Circulating levels increase after meals.
- Exendin 4: GLP-1 receptor agonist (first isolated from saliva of Gila monster lizard).
- **GLP-1 receptors** in CNS: especially brainstem (**DVC**) and hypothalamus (Arc) but also reward system. Acts as a **satiety signal.**
- Oxyntomodulin also binds to the GLP-1R
- **GLP-1 and oxytomodulin →↓ food intake and ↓food reward. ↓gastric motility.**
- Long-acting GLP-1 agonists now used clinically (e.g., Liraglutide, Semaglutide)
  - Improved glucose homeostasis (via its incretin effects – see glucose lecture from me).
  - **Weight loss**

Ozempic (Semaglutide) – anti-obesity drug

Long acting
GLP-1 analogue



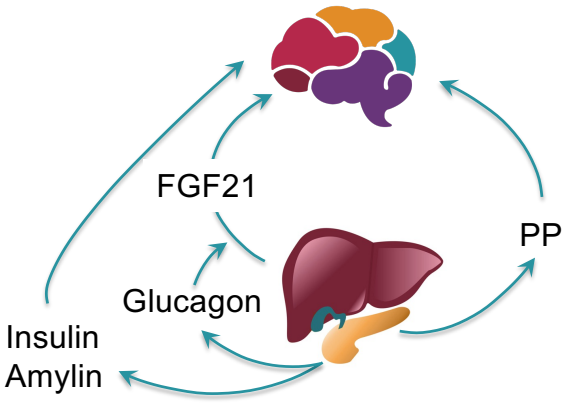
Gut peptides influencing energy balance
3. Cholecystokinin (CCK)

- Produced by **I cells** in the GI tract (eg duodenum and jejunum)
- Release increased especially by fat or protein in duodenum
- Causes meal termination (**satiation** signal)
- Also suppresses gastric emptying
- Two CCK receptors exist (CCK1 and CCK2) and can be found on vagal afferents as well as in relevant brain areas, especially brainstem (NTS, AP, Dra, the dorsal raphe) but also in reward areas.

Pancreatic hormones

- **Insulin and amylin. release from beta cells regulated by gut hormones** (especially GLP-1 and GIP).
- **Glucagon.** Increases FGF21 release from the **liver**.
- **Pancreatic polypeptide (PP)**

FGF21
- a hormone secreted by the liver
- regulates sugar intake and preferences for sweet foods via signaling through FGF21 receptors in the PVN (hypothalamus)



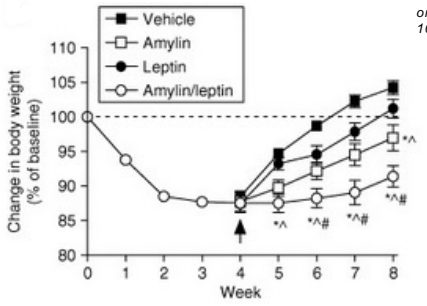
Pancreatic hormones and energy balance
1. Insulin

- Released in association with meals.
- Insulin receptors - hypothalamus (NPY, POMC) and brain stem (nucleus tractus solitarius).
- Direct brain action: Reduces food intake (and increases energy expenditure).
- May act as a **satiety signal**. Also provides a marker of fat mass (obese individuals have high levels).

Pancreatic hormones and energy balance
2. Amylin – a satiation signal?

- Produced by pancreatic beta cells
- Eating triggers release in proportion to caloric load
- When administered with leptin, a synergistic effect for weight loss was observed.
- Role: slows appearance of nutrients in blood after meals by (i) **↓food intake (decreased meal size),** (ii) slowing gastric emptying, (iii) inhibiting digestive secretions [gastric acid, pancreatic enzymes, and bile ejection].
- Centrally acting eg area postrema of the brain stem.

doi-org.ezproxy.ub.gu.se/10.1038/oby.2009.187

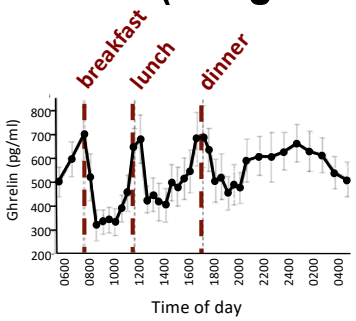


Maintenance of body weight loss induced by sustained infusion of amylin + leptin combination requires the presence of both amylin and leptin in diet-induced obese rats.

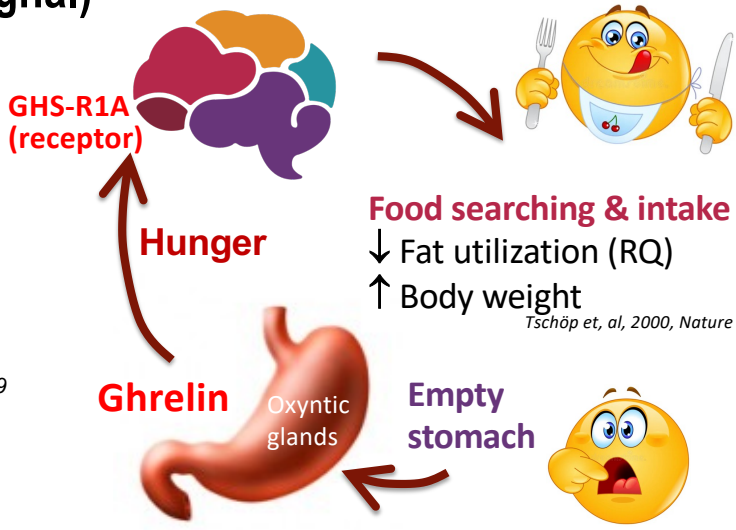
Pancreatic hormones and energy balance
3. Pancreatic polypeptide

- Released after a meal (and in proportion to caloric load) and reduces food intake acutely.
- **Satiation** signal?
- Chronic administration reduces body weight in genetically obese mice (ob/ob).
- Binds to neuropeptide Y4 and Y5 receptors.

Gut peptides influencing energy balance
4. Ghrelin (hunger signal)



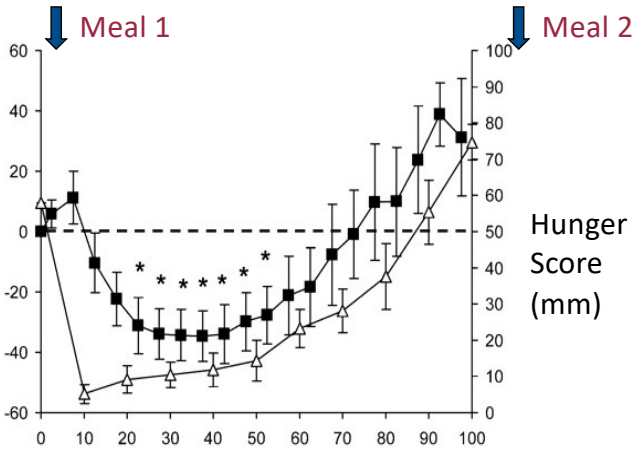
Cummings DE et al., 2001; Diabetes 50:1714-9



GHS-R1A = growth hormone secretagogue receptor 1A

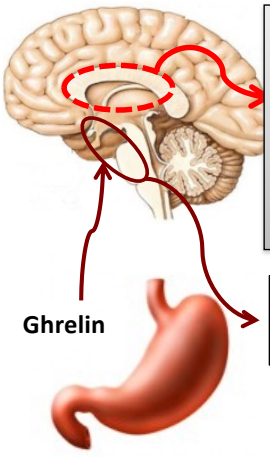
Ghrelin: the hormone that decides when you eat?

Cummings *et al*,
Am J Physiol
Endocrinol Metab



Ghrelin targets both homeostatic and reward systems to increase food intake and motivation

Main targets:



Reward system

Hypothalamus (especially Arc).

Many brainstem areas

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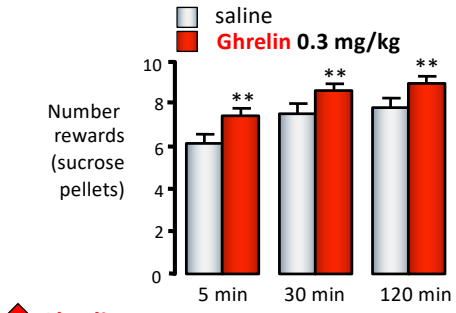
Ghrelin → Increased motivation to work for a food reward

How much work (number of lever presses) is a rat is willing to expend to obtain a sugar reward → an objective measure of reward value

Lever pressing for sucrose

FR1 → FR3 → FR5 → PR

Fixed Ratio → *Progressive Ratio*



Ghrelin

FULL/SATIATED RAT

FOOD REWARD & MOTIVATION

WORK TO RECEIVE SUGAR

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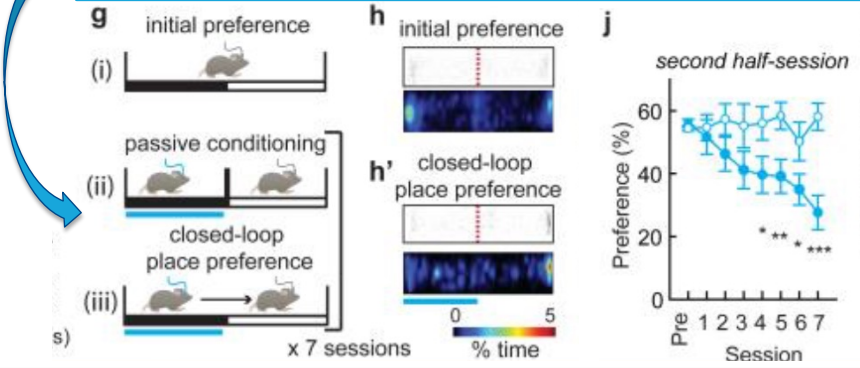
Ghrelin:

- Circulating stomach-derived hormone
- Produced by the **X/A-like cells** in the oxyntic glands
- The enzyme ghrelin-O-acetyltransferase (GOAT), present in these cells, is responsible for acylating ghrelin on serene 3 (makes it active).
- Increases food intake and food seeking.
- Ghrelin receptor (**GHS-R1A**) located in brain areas controlling
  - energy balance (eg hypothalamus, brain stem),
  - reward (eg tegmental areas such as the VTA)
  - also amygdala, hippocampus
- **Physiological role: meal initiation, hunger, reward-seeking (eg for food).**
- Obesity is not associated with hyperghrelinaemia.
- May be relevant for eating disorders, including those that lead to obesity.

AgRP neurones (a target for ghrelin) signal the unpleasantness of hunger.

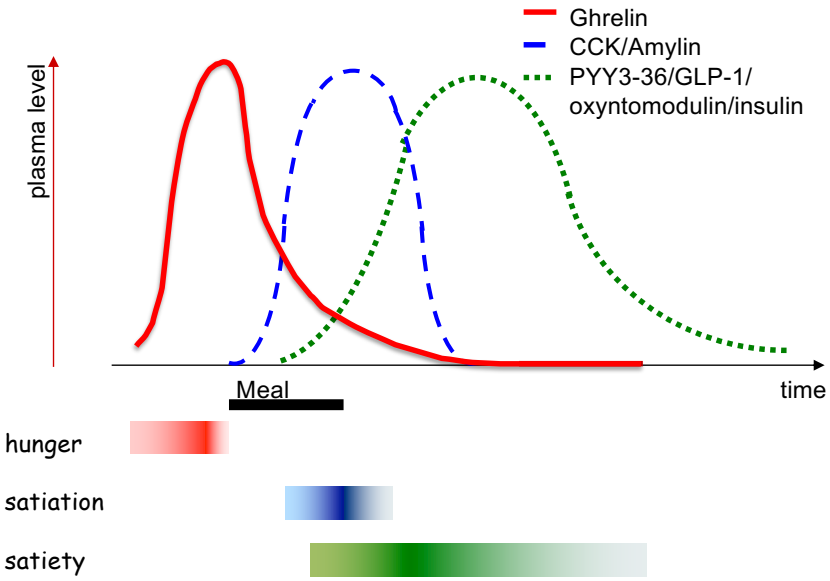
doi: 10.1038/nature14416

Method: Optogenetic activation if AgRP neurones when mice are in the left (Blue) chamber. **Result.** With each of 7 (15 min) sessions they increasingly avoid the chamber in which their AgRP neurones were activated.



Conclusion:
Mice dislike having their AgRP neurones activated. Likely they are experiencing the unpleasantness of hunger.

Appetite-regulating hormones signal hunger, satiation and satiety



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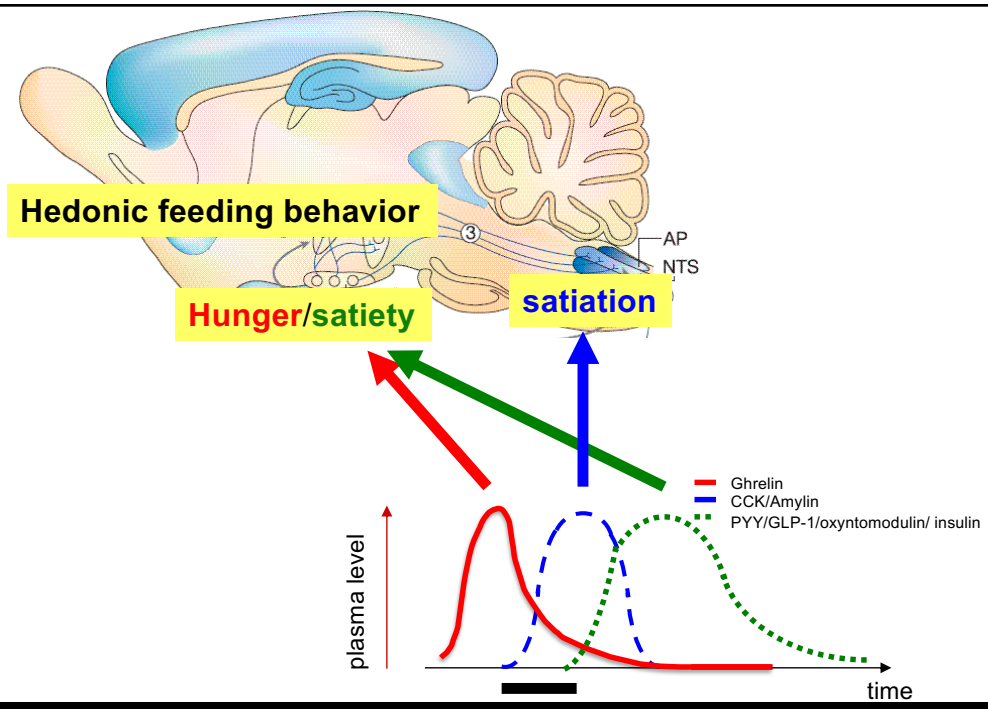


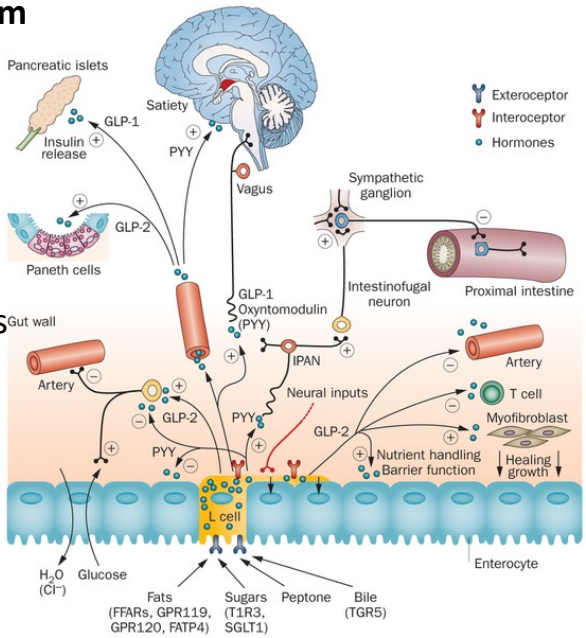
100

Endocrine intestinal cells sense nutrients and signal directly to the nervous system

Brain

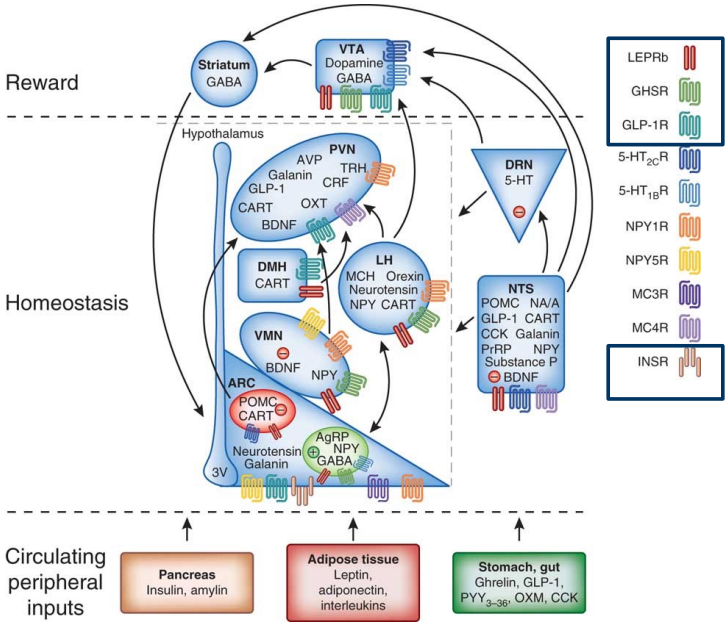
Gut hormones

Nutrient sensing



DOI:10.1038/nn.3211

Several neural circuits respond directly to hormones from intestine, fat, and pancreas



•DOI:10.1038/nn.3211

So, what causes obesity and what can we do about it?

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How much obesity is genetics and how much is environmental?

EndocrineWebPro

Arguing for a genetics component:

- People in same environment don't necessarily have same body weight
- The remarkable increase in obesity trends over last few decades cannot be only due to genetics.
- Some ethnic groups are more likely to develop obesity)
- There have always been some people predisposed to weight gain
- Data from twin and adoption studies
- Heritability of body weight is 70% (almost as much as that of height 85%)

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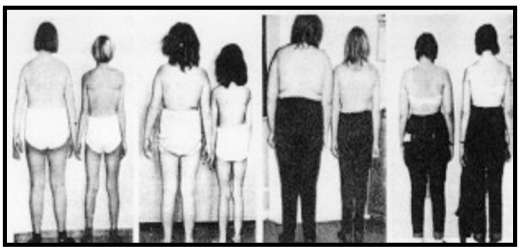
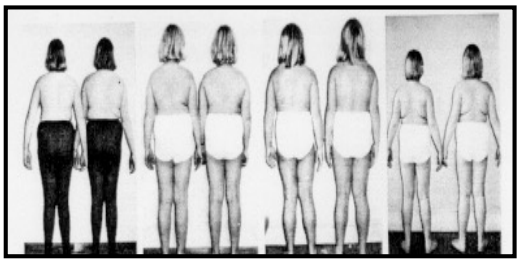
Genetics of obesity: twin studies



Dizygotic Twins

Heritability estimates

#0.6-0.8



Monozygotic Twins

Wardle J et al Am Clin Nutr 2008 Heritability of childhood BMI in UK – 75%

Genetics of obesity- interaction with environment

- Genetic factors contribute 40-70% to excess body fat.
- Pima Indians – nomads - scarce conditions but develop obesity when food is available.
- "**Thrifty genotype**" hypothesis. Certain genes in humans have evolved to maximize metabolic efficiency and fat storage. In times of plenty, these genes predispose their carriers to obesity and diabetes.
- Environment gives genetics (Darwin)

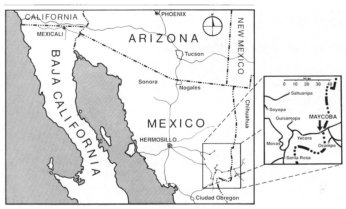


Figure 1—*Map of southern Arizona and northern Mexico showing where the Pima Indians live. The Pima Indians of the Gila River Indian Reservation live ~60 km southeast of Phoenix, whereas the Pima Indians living in Sonora live 340 km southeast of Hermosillo.*

Ravussin E et al., Diabetes Care 1994

Figure 4—*The remote village of Maycoba in Sonora has no running water and no electricity. Here, Pima women wash clothes in the stream.*

Figure 2—*A typical three-generation family of Pima Indians living on the Gila River Indian Reservation in Arizona.*

Genetics of obesity: known genes that contribute

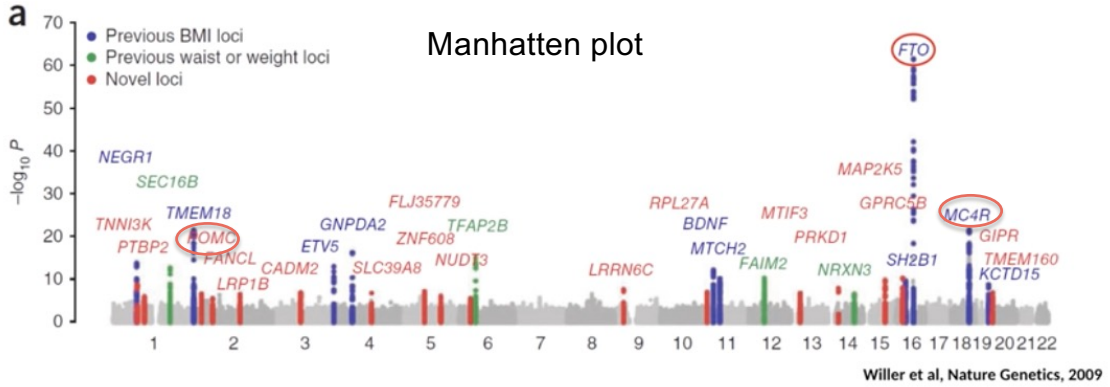
- Few obesity genes known yet (less than 5% of genetically determined obesity).
- Monogenic causes (eg gene deletions) rare
  - **POMC/MC4-R** deletions - MC4-R; heterozygotes have "middle" phenotype.
  - **Leptin/leptin receptor** dysfunction
- >300 SNPs linked to obesity traits, emerging from GWAS. Most still of unclear biological significance (eg **FTO**). The association of the *FTO* region to obesity explains ~1% of BMI heritability, such that adults homozygous for the risk allele, have a 2–3 kg higher weight compared to non-risk allele homozygous (*Frayling TM et al., 2007*)

FTO = FaT mass and Obesity-associated protein

- Subtle changes in individual genes impact on body weight.
- The more risk alleles you have the more likely you will have a high BMI
- Many risk alleles are hypothalamic.

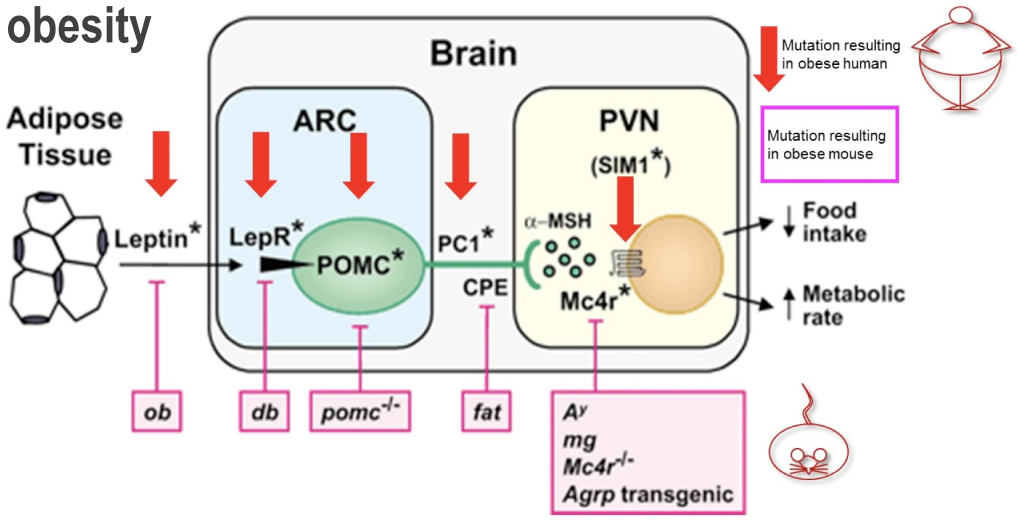
Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

Manhatten plot



Willer et al, Nature Genetics, 2009

Disruption of melanocortin signalling causes severe obesity



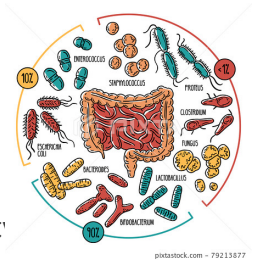
Note, semaglutide is a recently approved drug for obesity that is caused by gene defects upstream of MC4R

Source: Giles Yeo

Epigenetics factors and Obesity

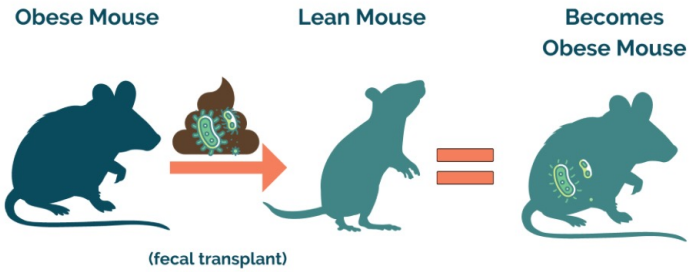
- **Epigenetics** - the study of heritable changes which affect gene function without modifying the DNA sequence.
- Epigenetic markers are tissue specific and include **DNA methylation** and **histone modifications** which mediate biological processes such as imprinting. (Note FTO codes for a DNA methylase that turns off genes)
- **Hypothesis:** early environmental influences induce epigenetic variation, thereby permanently affecting metabolism and chronic disease risk.
- Eg Epigenetic factors may explain why under or over-nutrition in utero (environment) → ↑ risk of metabolic disease in later life.

Gut microbiota and obesity

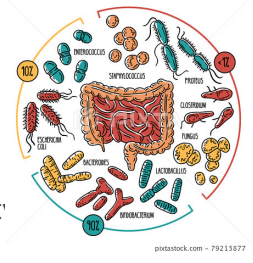


- The human gut has a diverse microbial ecosystem (>2000 different species, high inter-individual variability).
- **Hypothesis:** Gut microbiota contribute to the development of obesit metabolic syndrome.

Evidence: Transplantation of gut microbiota from obese mice to non-obese, germ-free mice resulted in transfer of metabolic syndrome-associated features from the donor to the recipient.



Gut microbiota and obesity



- The human gut has a diverse microbial ecosystem (>2000 different species, high inter-individual variability).
- **Hypothesis:** Gut microbiota contribute to the development of obesit metabolic syndrome.
- **Evidence:** Transplantation of gut microbiota from obese mice to non-obese, germ-free mice resulted in transfer of metabolic syndrome-associated features from the donor to the recipient.
- Mechanism currently being researched
  - provision of additional energy by the conversion of dietary fiber to short-chain fatty acids?
  - effects on gut-hormone production?
  - ↑ intestinal permeability → systemic levels of lipopolysaccharides (LPS → low-grade inflammation (as seen in obesity/metabolic syndrome)?

But what about dietary control?

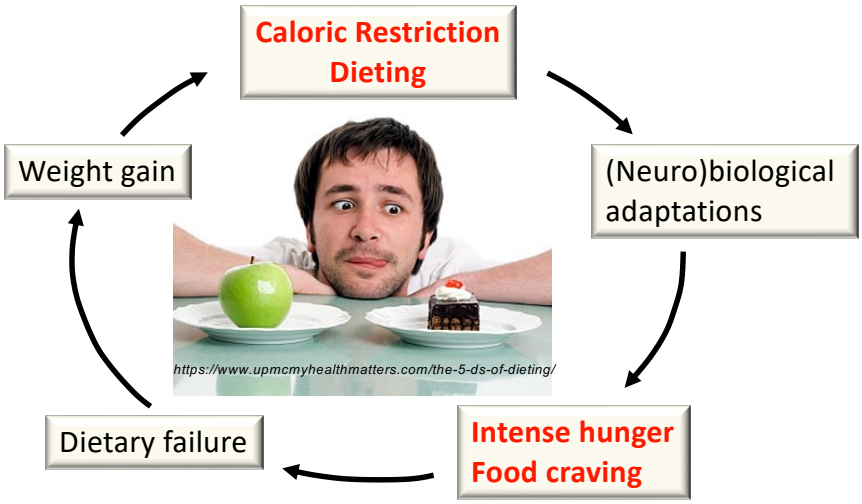
- We have evolved to over-eat available foods to prepare for a future famine.
- People with genetic obesity are fighting their biology. Prone to make unhealthy decisions around food, for example.
- Obesogenic caloric foods are energy-dense and it is easy to overconsume them, even when full.
- All diets that reduce caloric intake or decrease energy expenditure work – if we keep to them. Why do they fail?

Dessert when full

The happyfoodie.co.uk

Why don't diets work?

- Decreased leptin is important when dieting – turns on the **starvation response**: over-eating, ↑ reward value of food, save energy for brain, switch off costly energy functions (e.g. reproduction, immune system).
- The threshold to respond to a dieting-induced fall in circulating leptin may be higher in obese individuals, making it hard for them to reduce food intake.
- When hungry (or dieting) food cues are increasingly attractive and it becomes hard to resist food.



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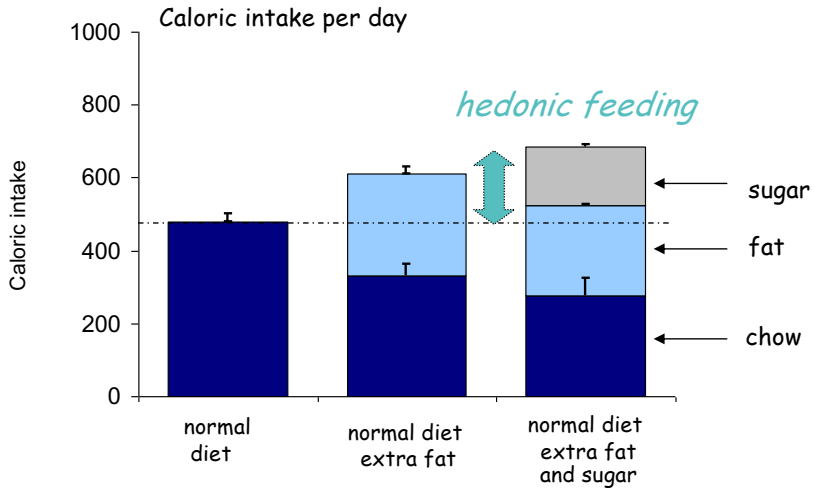
The more to choose, the more calories are eaten



Study in rodents given choice diets.

Adan RA & LaFleur SE

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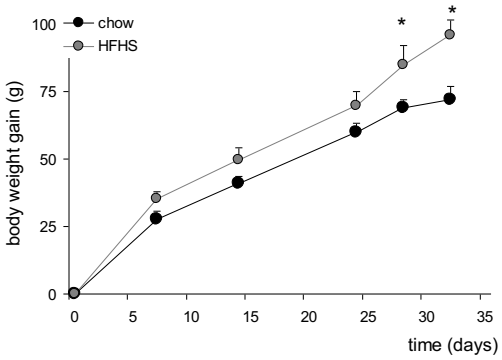
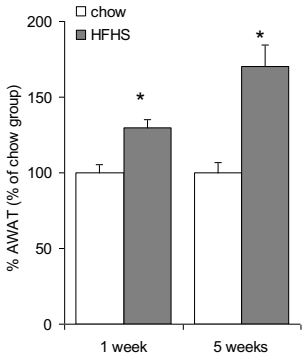
Animals on a high fat-high sugar (HFHS) diet gain weight





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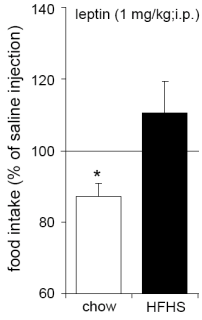
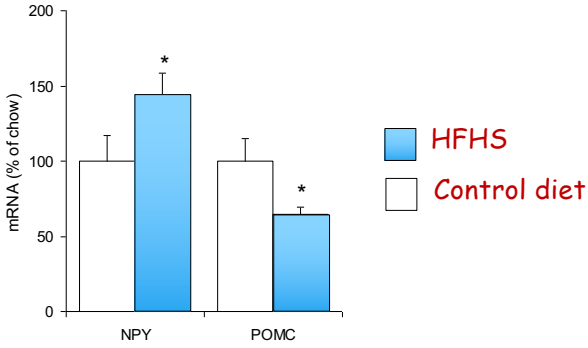
Animals on a high fat-high sugar (HFHS) diet become leptin resistant & have a "hungry" neuropeptide profile

Effect of leptin injection on food intake



HFHS-choice diet: insensitive to leptin – it doesn't suppress food intake



HFHS-choice diet: hypothalamic gene changes similar to hunger → eat more!

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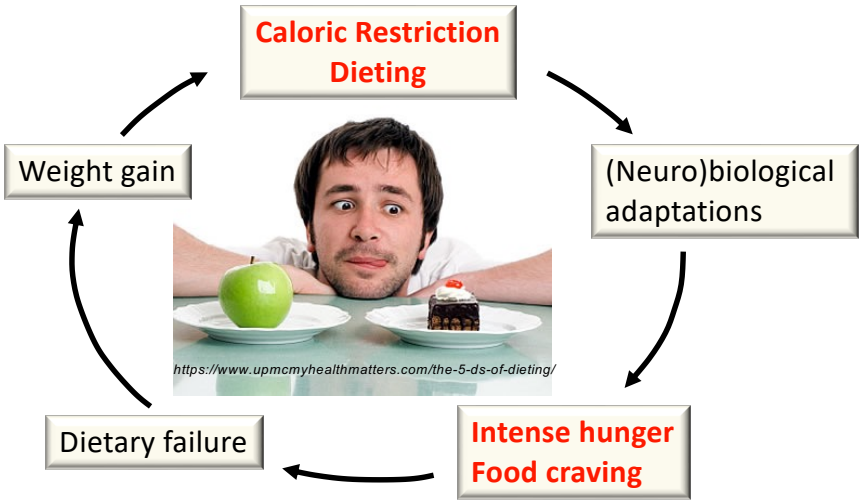
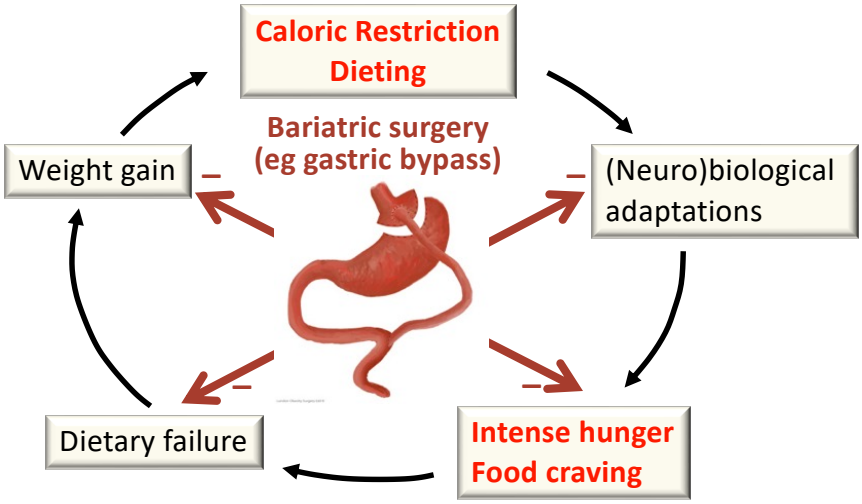


How can we break the cycle?

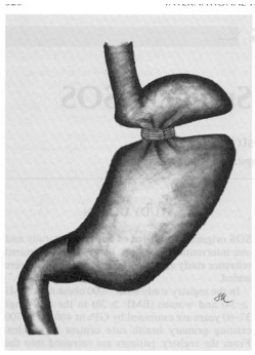
Breaking the viscous cycle of weight gain: bariatric surgery → improved food reward control



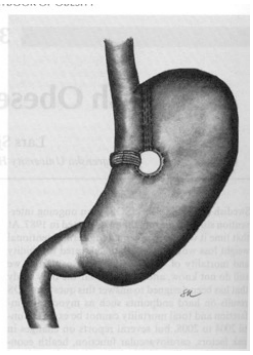
We need to understand how/why bariatric surgery works

Bariatric (weight loss) surgery

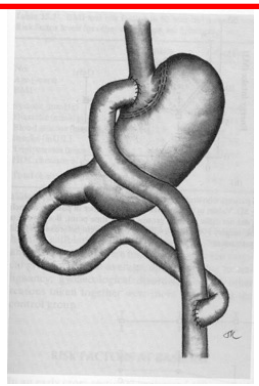
Only effective Obesity therapy



Gastric banding



Vertical banded gastroplasty



Gastric bypass

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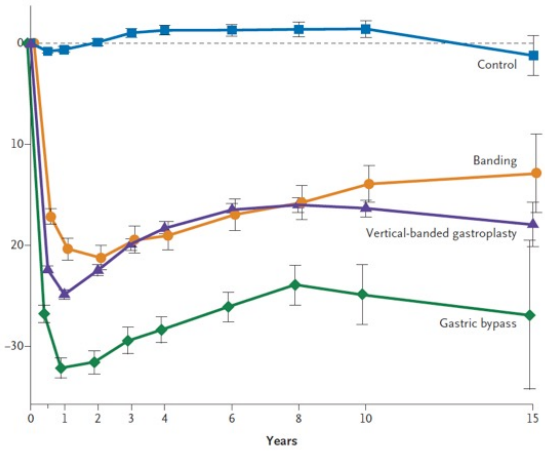
Swedish Obese Subject study: Weight loss after bariatric surgeries

Change in Body Weight (%)



control

banding

Ventral-banded gastroplasty

Gastric bypass

No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

Sjöström L et al NEJM 2004

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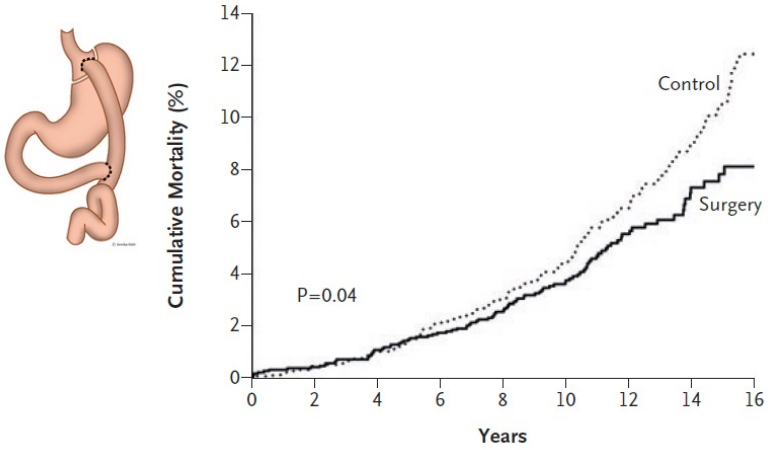
Swedish Obese Subject study: Mortality



Gastric bypass surgery → weight loss and reduced mortality. **Life expectancy ↑ by 12 years.**

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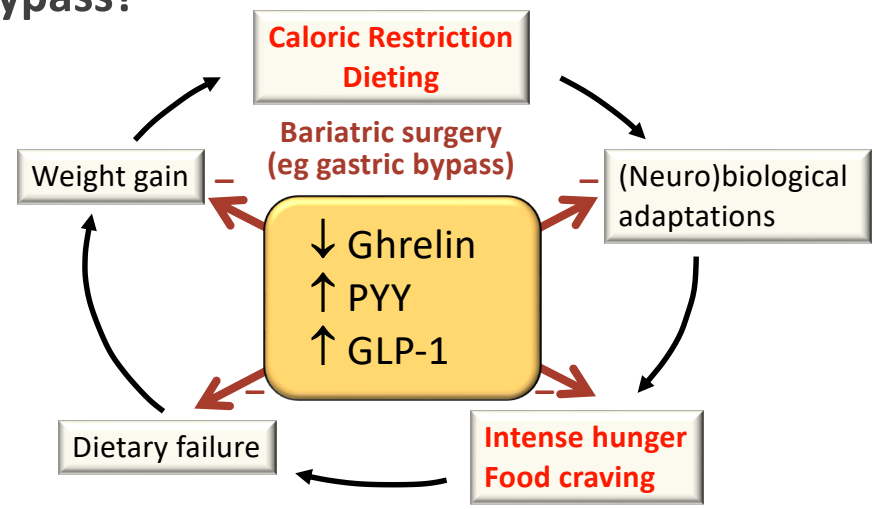
The future: Novel obesity therapies that "bypass" gastric bypass?



It is not yet clear that these changes in hormone levels are important for the weight loss after gastric bypass!!!

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Gastric Bypass surgery: Physiology

Food enters small gastric pouch → fullness sensed (**nervous**)
Discomfort & vomiting if over-eat.
When food enters small intestine → **Anorexigenic hormones released**
eg CCK (duodenum), GLP-1 & PYY(3-36) (ileum)

Mechanism

Decreased **container function** /restriction? Probably not – other restrictive procedures are less effective.
Malabsorption? Certainly not a primary mechanism.
Increased **energy expenditure** (eg could involve increased bile salts taken up into blood).
Increased **anorexigenic signals** after meals and/or decreased **ghrelin** before meals? Hormones likely contribute to weight loss success.
Improved **food choice** – brain reward system implicated.
Others? Eg microbiota, nutrient sensing by gut.

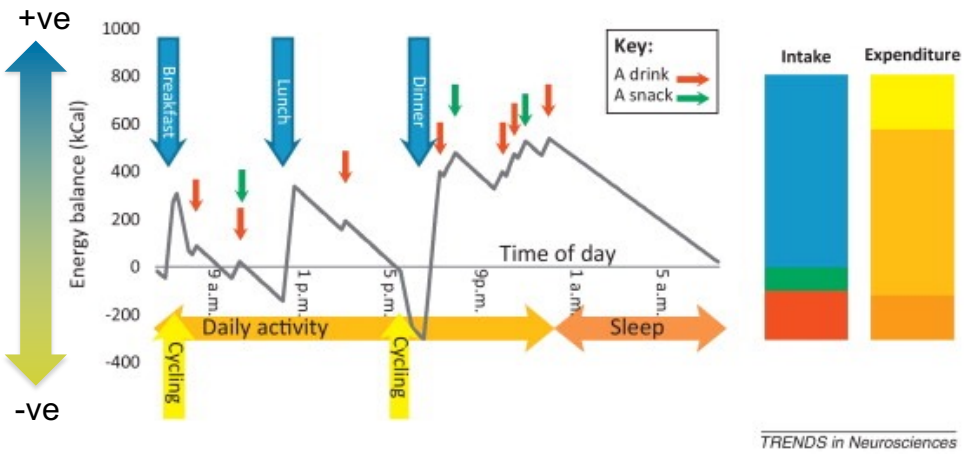
… actually … we don't really know.

Anti-obesity drugs: possible mechanisms?

- Decrease food intake (reduce hunger, reduce reward, increase satiety, delay meal initiation, reduce portion size, improve choice)
- Decrease gut uptake of nutrients
- Increase energy expenditure (ie the use of energy by the body).

Longterm effects only persist if we can reduce the "set point" (ie make an individual percieve their energy homeostasis to be set at a level lower that it is).

Energy Balance Fluctuations Over a Day



Preventative and treatment strategies for obesity should target especially food intake.