

Regulation of food consumption energy surplus

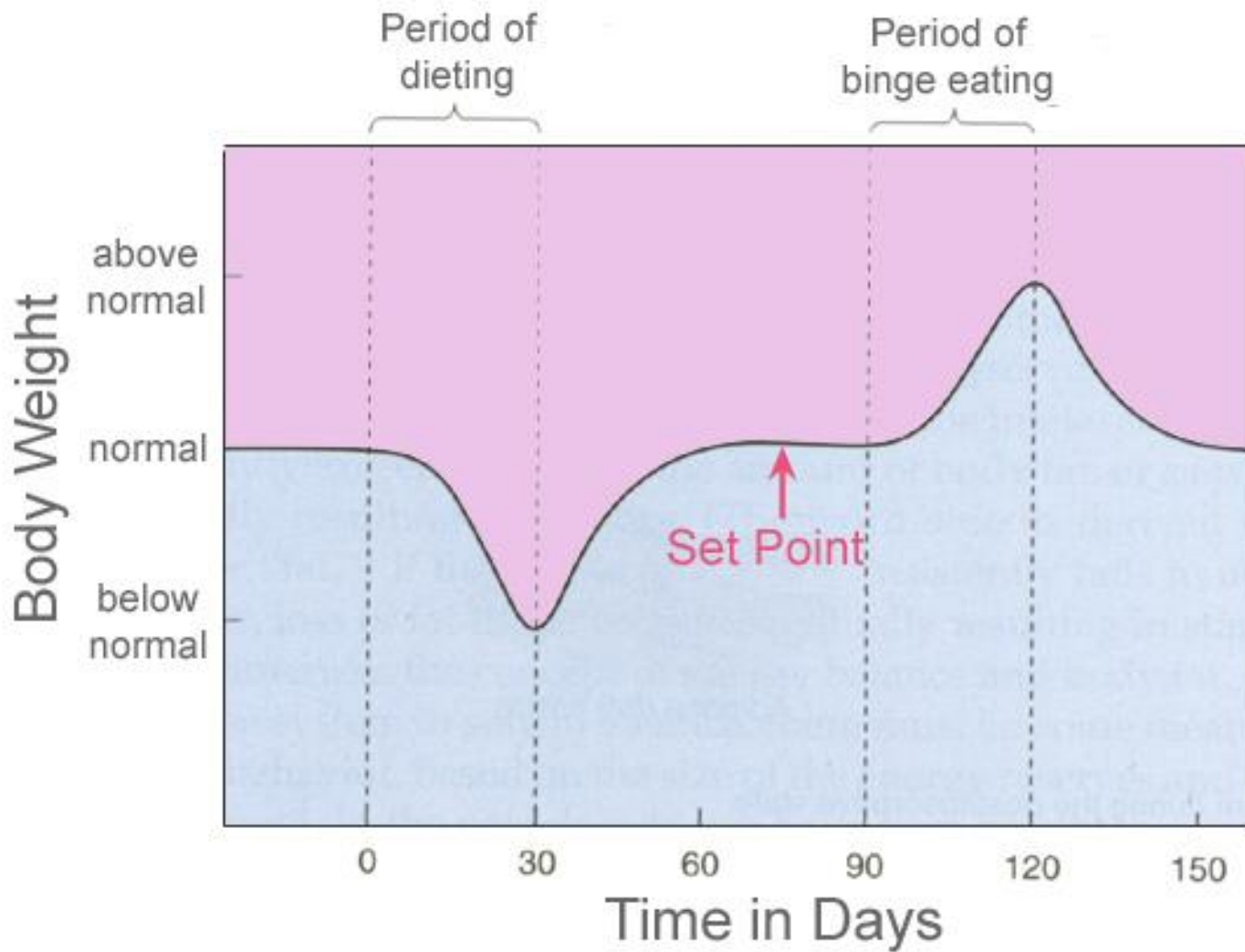
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| Food | (a) kcal g ⁻¹ | (kJ g ⁻¹) | (b) liter O ₂ g ⁻¹ | (c) kcal per liter O ₂ | (kJ per liter O ₂) | (d) $RQ = \frac{CO_2 \text{ formed}}{O_2 \text{ used}}$ |
|---------------------|-----------------------------|-----------------------|---|---|-----------------------------------|--|
| Carbohydrate | 4.2 | (17.6) | 0.84 | 5.0 | (20.9) | 1.00 |
| Fat | 9.4 | (39.3) | 2.0 | 4.7 | (19.7) | 0.71 |
| Protein (urea) | 4.3 | (18.0) | 0.96 | 4.5 | (18.8) | 0.81 |
| Protein (uric acid) | 4.25 | (17.8) | 0.97 | 4.4 | (18.4) | 0.74 |

Table 5.1 Heat produced and oxygen consumed in the metabolism of common foodstuffs. The values for protein depend on whether the metabolic end product is urea or uric acid. The ratio between carbon dioxide formed and

oxygen used is known as the respiratory quotient (RQ).
[Data based on Lusk 1931; King 1957]

| | gr/KCal |
|---------------------|-------------|
| Fat | 0.11 |
| Protein | 0.23 |
| Carbohydrate | 0.24 |
| Glycogen | 1.00 |



Advantages of keeping steady levels of energy sources.
Not less, not more.

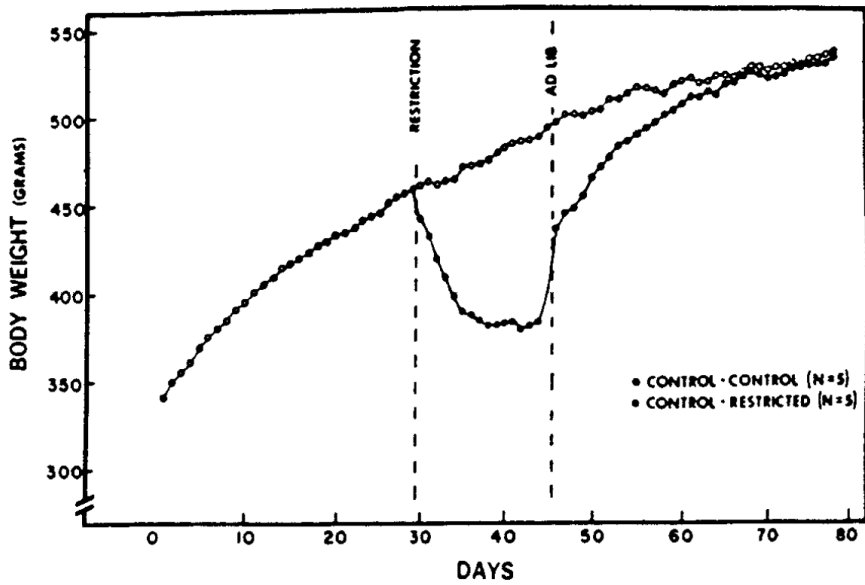
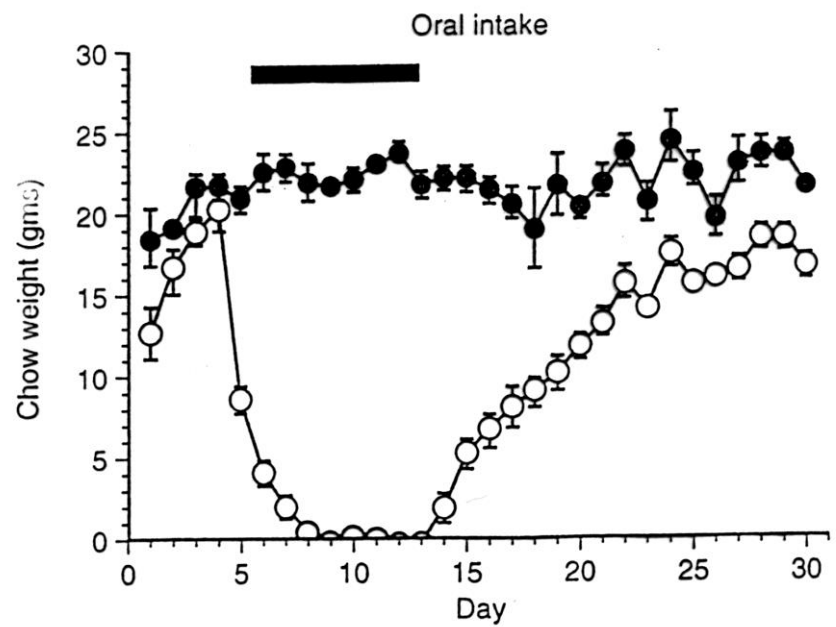
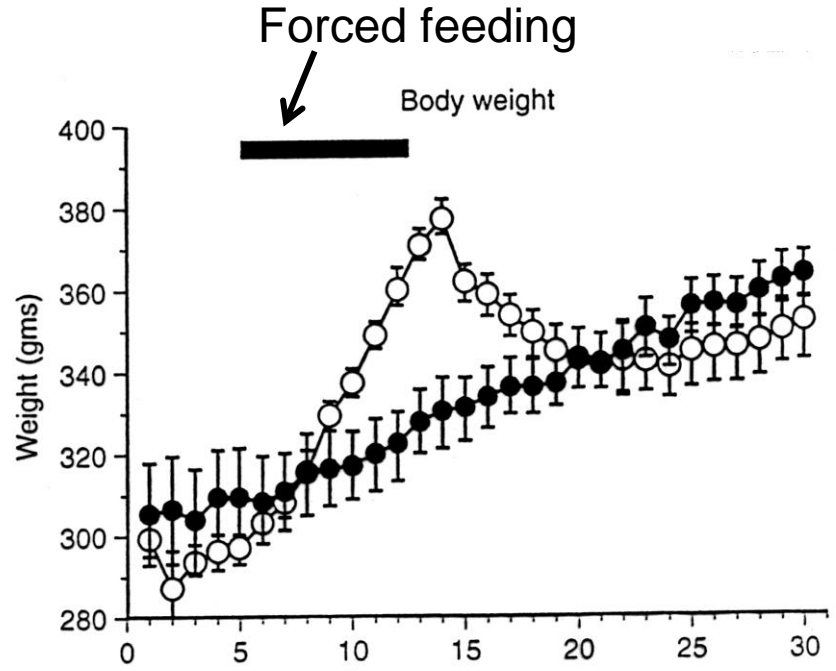
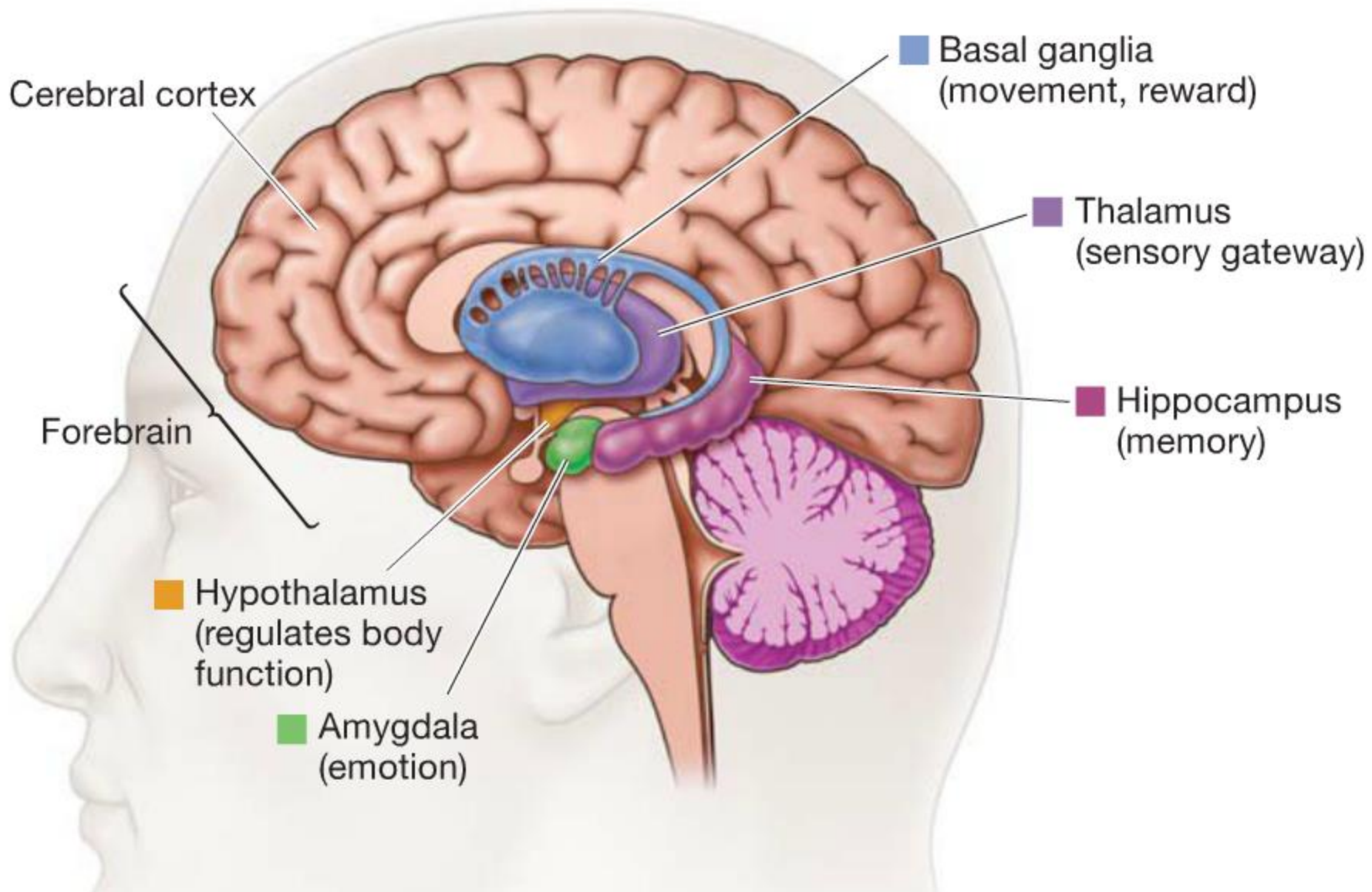


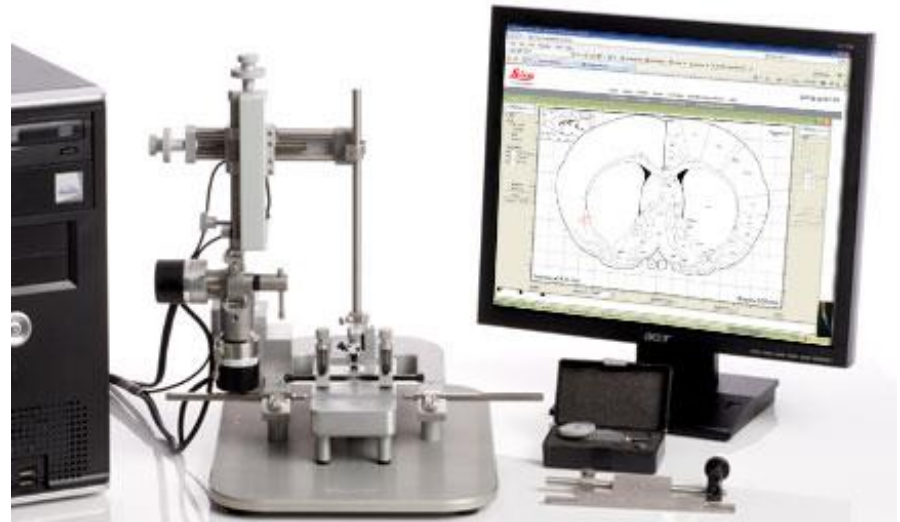
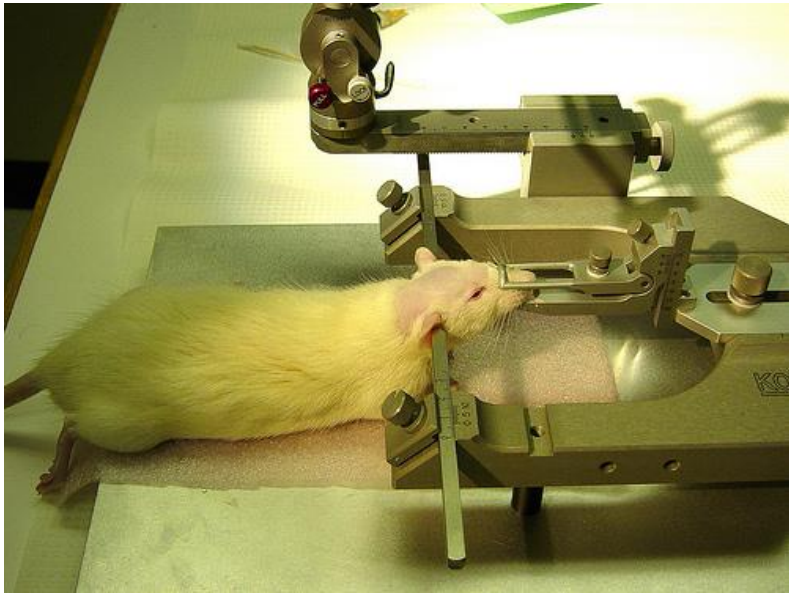
FIGURE 1 Recovery of body weight by rats after a period of caloric restriction [adapted with permission from Mitchel and Keesey (1977)].



The **lipostatic hypothesis**. Body weight and fat mass stays constant by hypothalamic control. The hypothalamus senses to the concentration of a metabolites in the circulation and regulates the amount of energy surplus.

Kennedy, 1953





The Hypothalamus

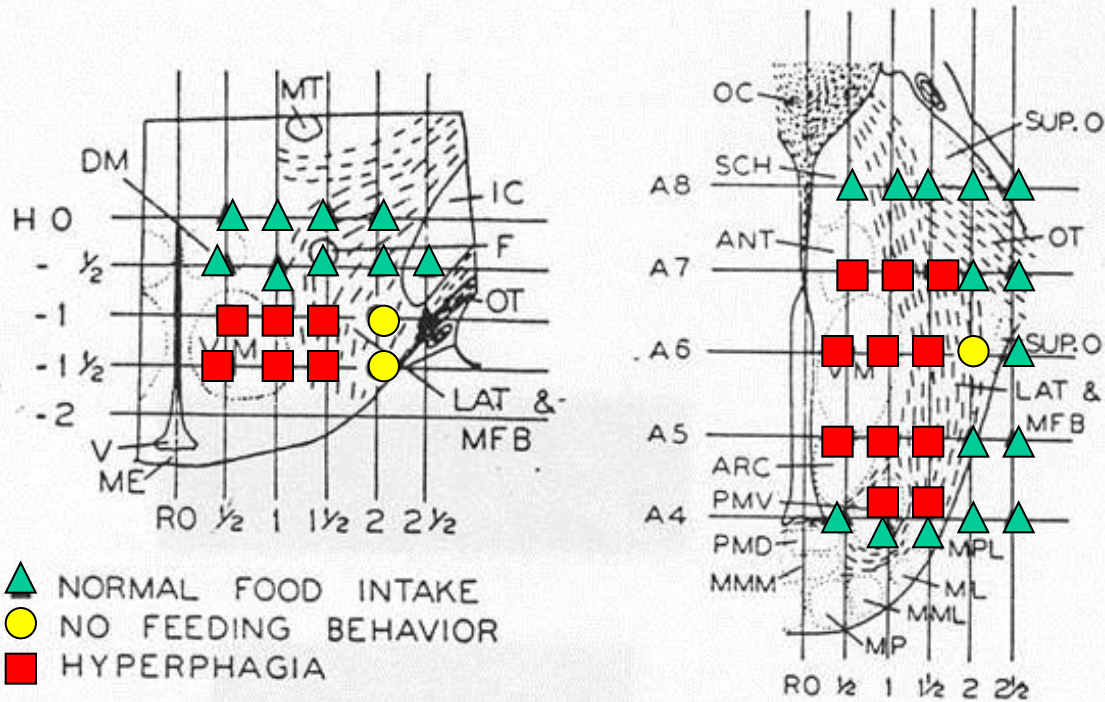
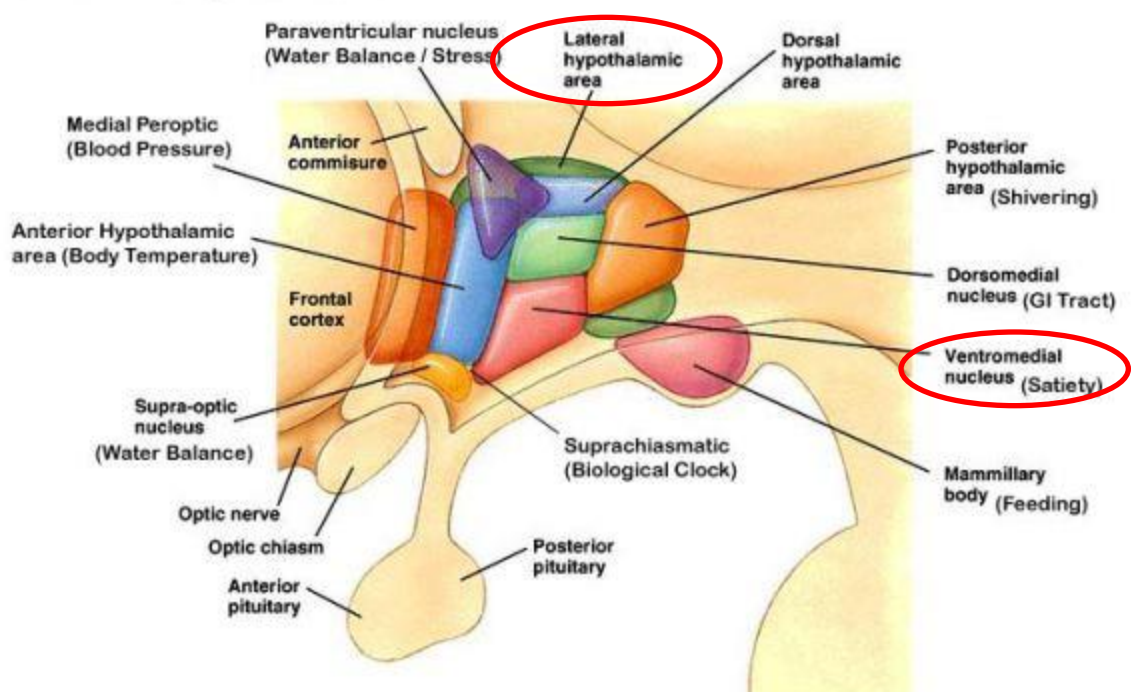
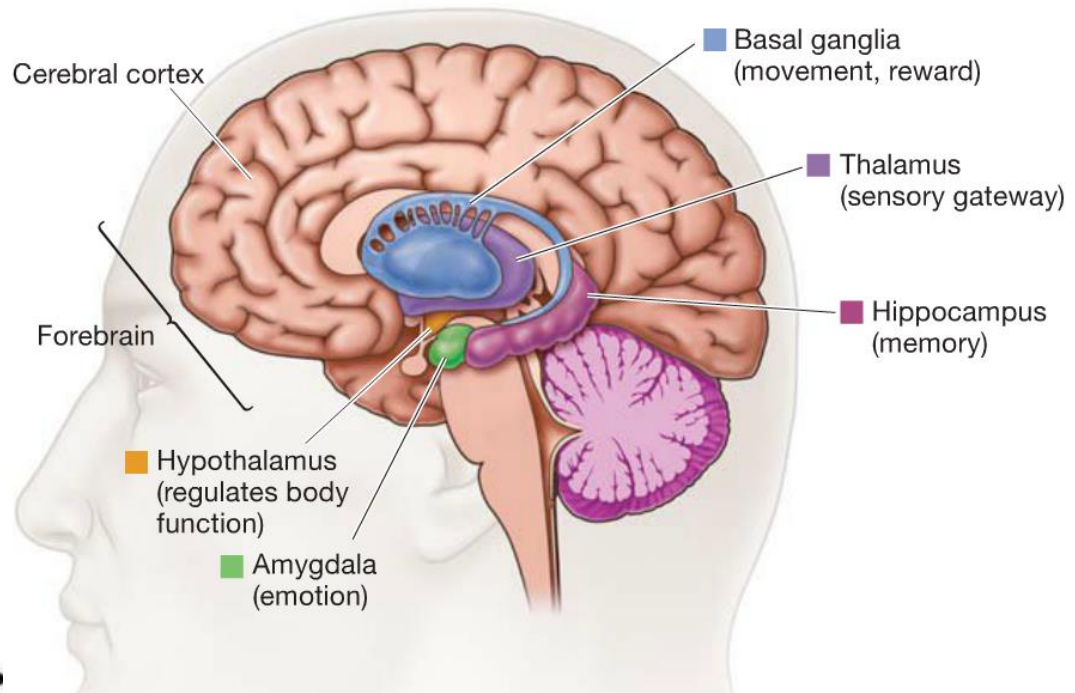
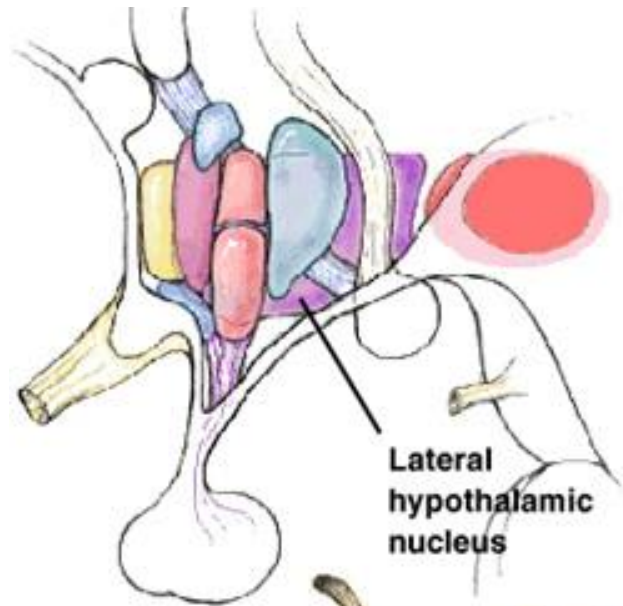
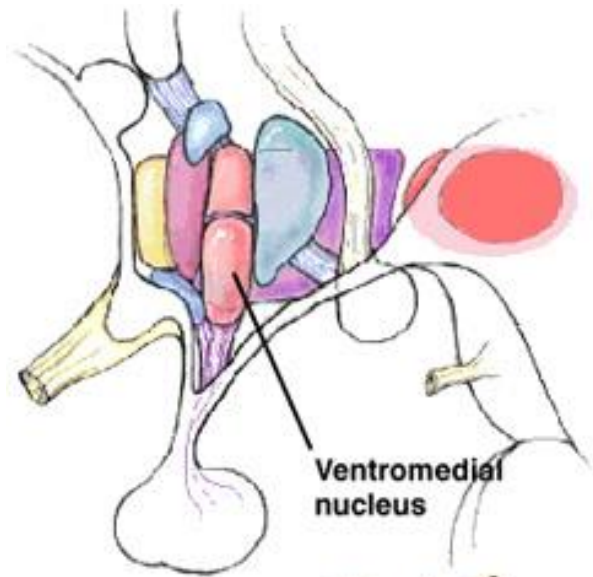


FIGURE 15-4. Cross section of a rat's hypothalamus at level of the ventromedial nucleus (*left*) and of the same side in a horizontal plane, also at the level of the ventromedial nucleus (*right*). Horsley-Clarke coordinates are superimposed. The feeding behavior of rats with small bilaterally symmetrical lesions in each area is indicated. (From Anand and Brobeck,¹⁶ courtesy of *Yale J. Biol. Med.*)





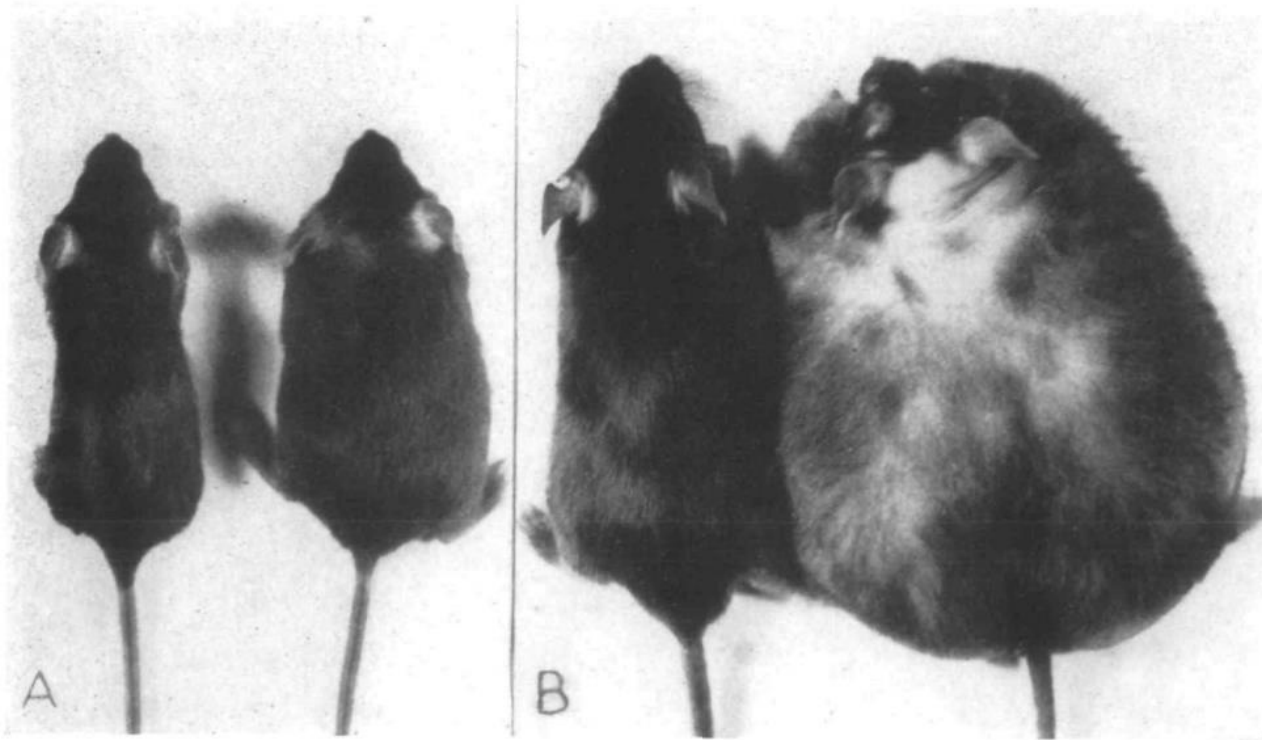
The **lipostatic hypothesis**. Body weight and fat mass stays constant by hypothalamic control. The hypothalamus senses to the concentration of a metabolites in the circulation and regulates the amount of energy surplus.

Kennedy, 1953



OBESE, A NEW MUTATION IN THE HOUSE MOUSE*

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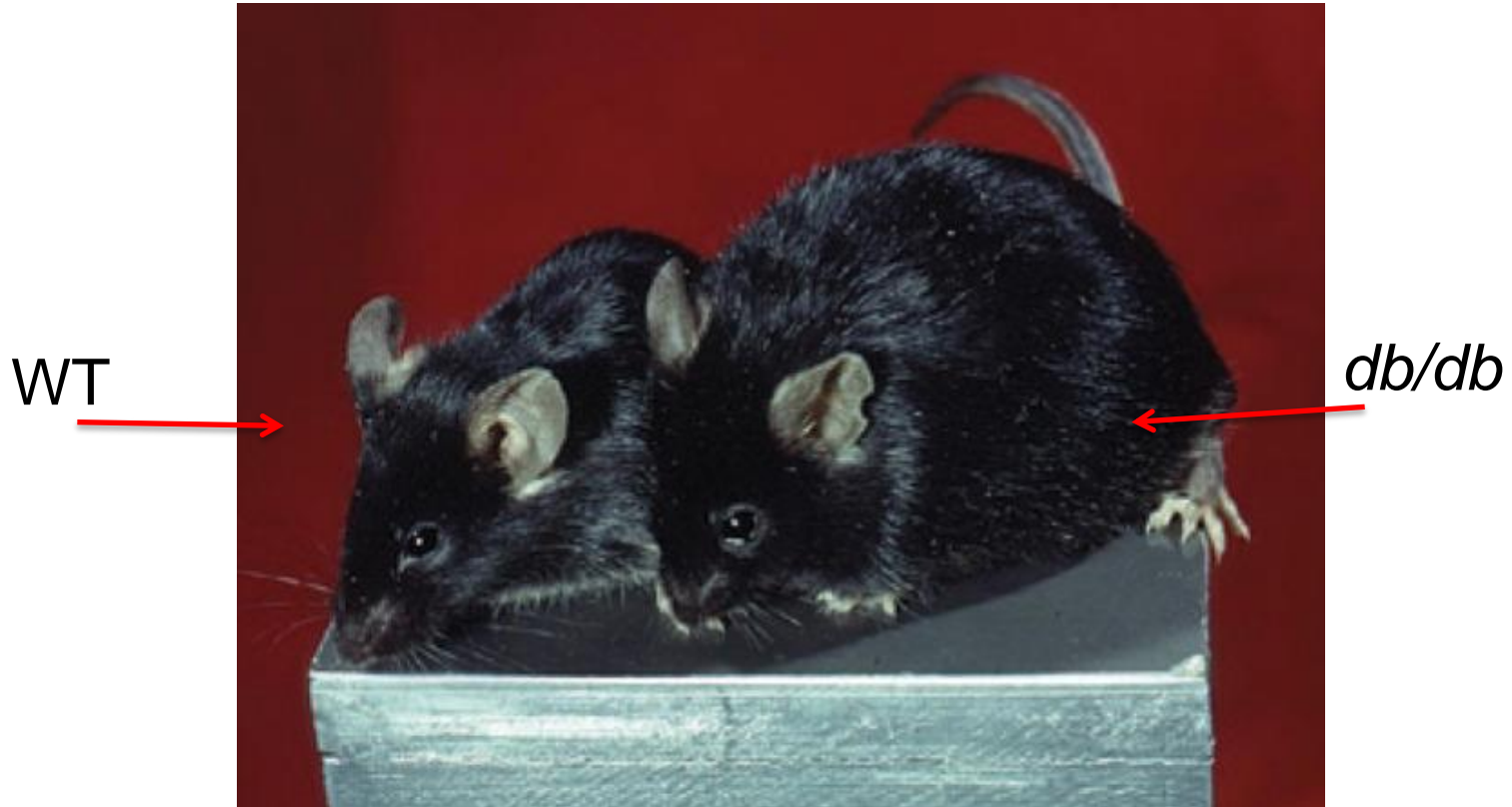
THE FAT MOUSE GROWS UP

Figure 4

A—shows normal control and an obese mouse at 21 days of age. The former weighed 12 grams; the latter 16. *B* shows a normal and obese mouse at ten months of age, when the obese mouse weighed 90 grams and the normal mouse 29 grams.

The *ob* mutant is characterized by massive obesity, marked hyperphagia, mild diabetes and infertility

db/db mutant mouse



The *db* (diabetes) mutant, like the *ob/ob* mouse, develops marked obesity and hyperphagia. It also develops severe, life-shortening diabetes.

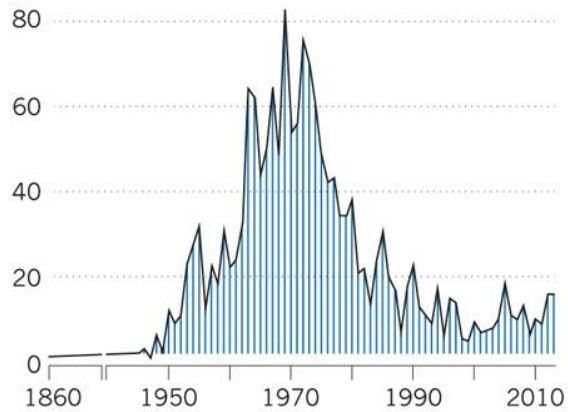
Parabiotic experiments

Share and share alike

Parabiotic experiments, in which two animals share a common bloodstream, were first attempted in the 1860s. By connecting animals with different qualities or conditions, scientists can investigate how blood factors, such as cells, proteins or hormones, influence health. In recent years, a few researchers have looked at heterochronic (old and young) mouse pairs to understand how young blood helps to repair many tissues.

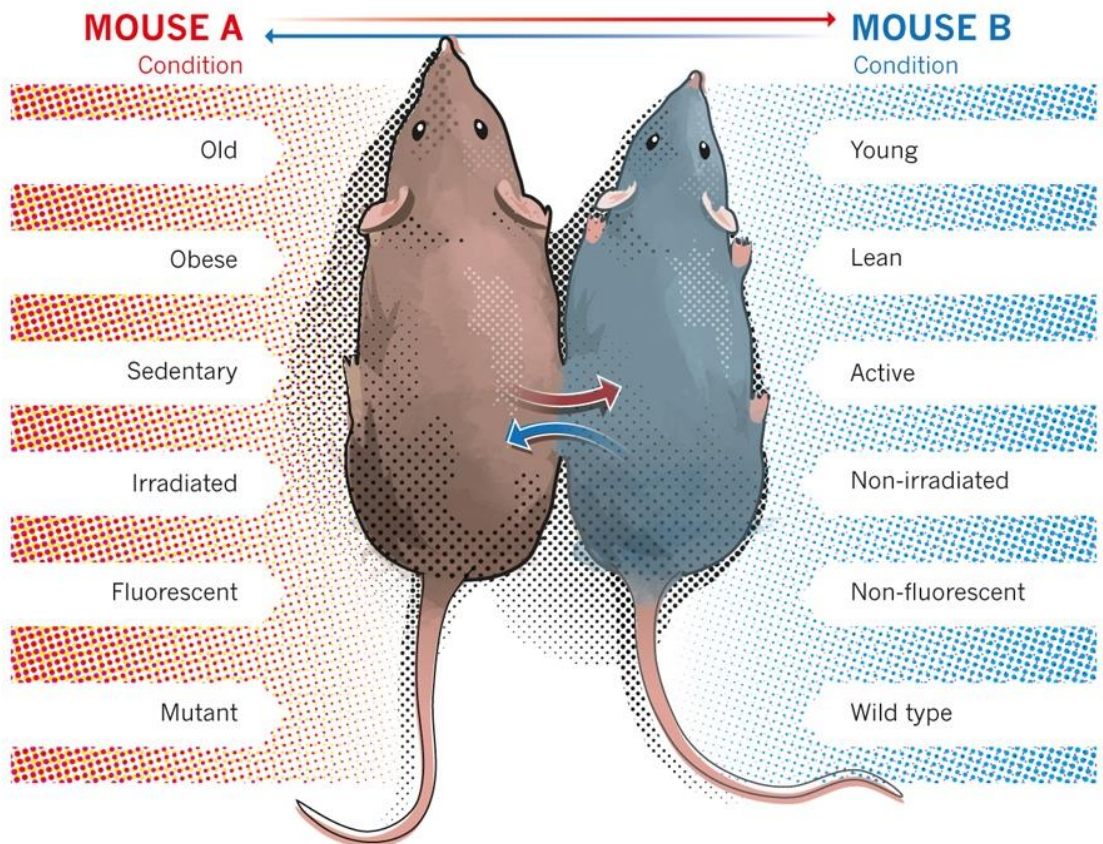
Publications on parabiosis

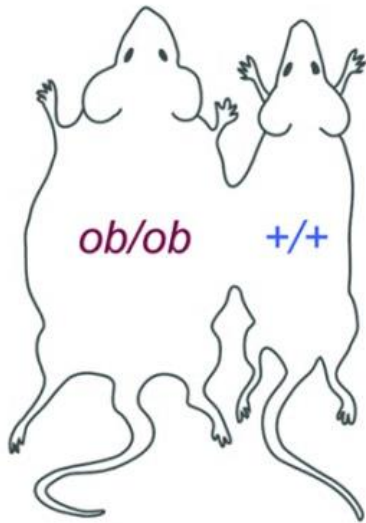
Parabiosis gained popularity during the 1960s and 1970s, but eventually fell out of wide practice.



A simple surgery

A veterinary surgeon will anaesthetize the animals, peel away a thin layer of skin along their sides and stitch or staple the exposed surfaces together. Wound-healing processes join the bloodstreams through a capillary network, and in one to two weeks, the animals are pumping each other's blood.



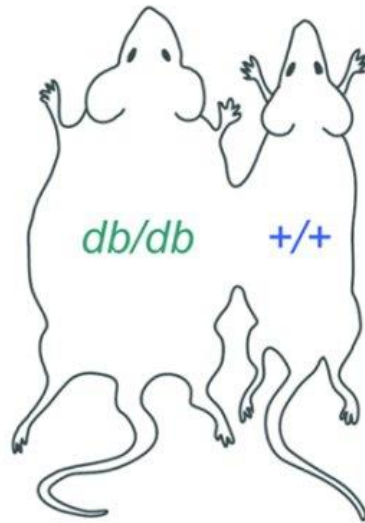


Obese

- ↓ Food intake
- ↓ Insulinemia
- ↓ Blood sugar

Wild type

No change

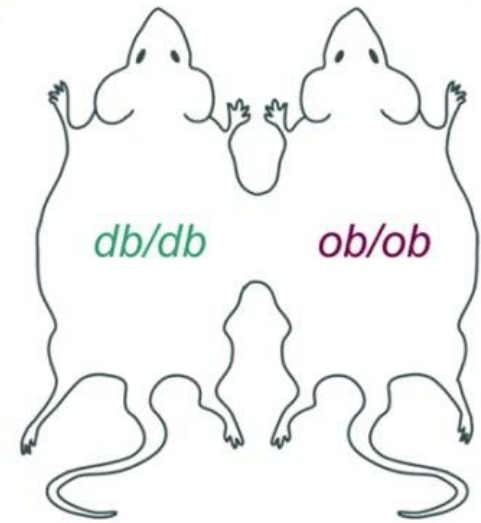


Diabetes

- ↑ Body weight
- ↑ Adipose tissue mass

Wild type

- ↓ Food intake
- ↓ Insulinemia
- ↓ Blood sugar
- Death by starvation

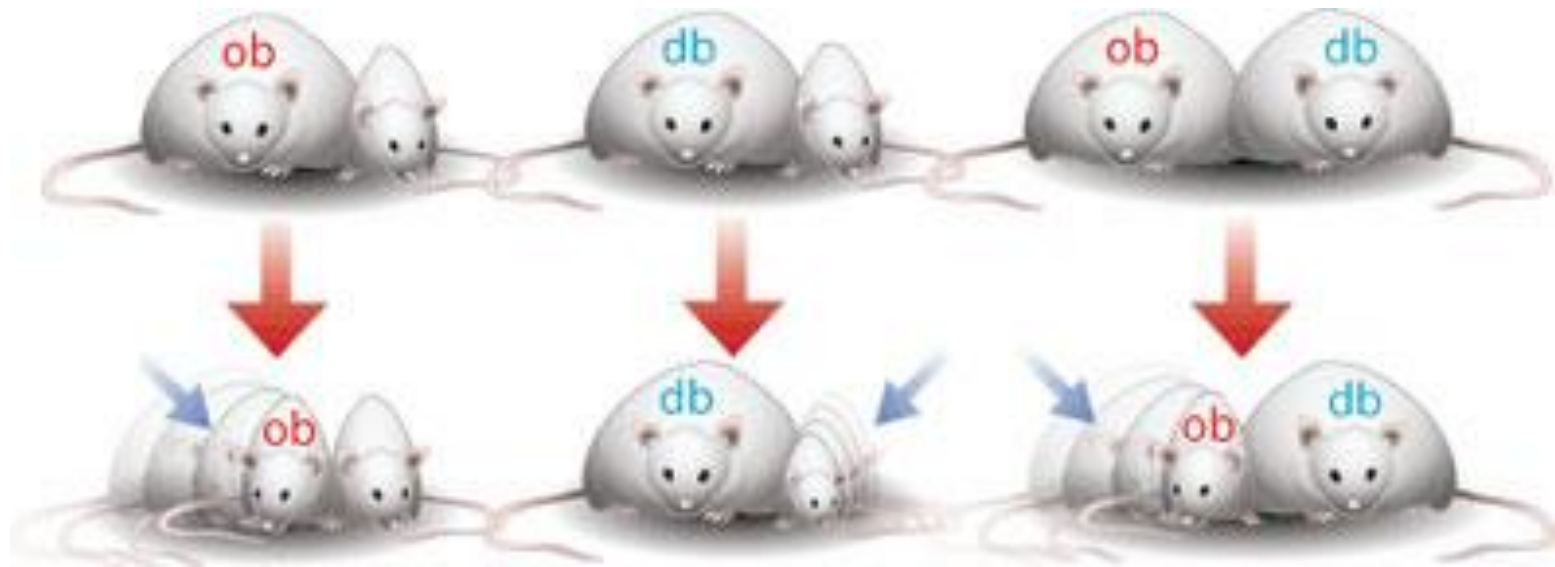


Diabetes

- ↑ Body weight
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Obese

- ↓ Food intake
- ↓ Body weight
- ↓ Adipose tissue mass
- ↓ Insulinemia
- ↓ Blood sugar
- Death by starvation



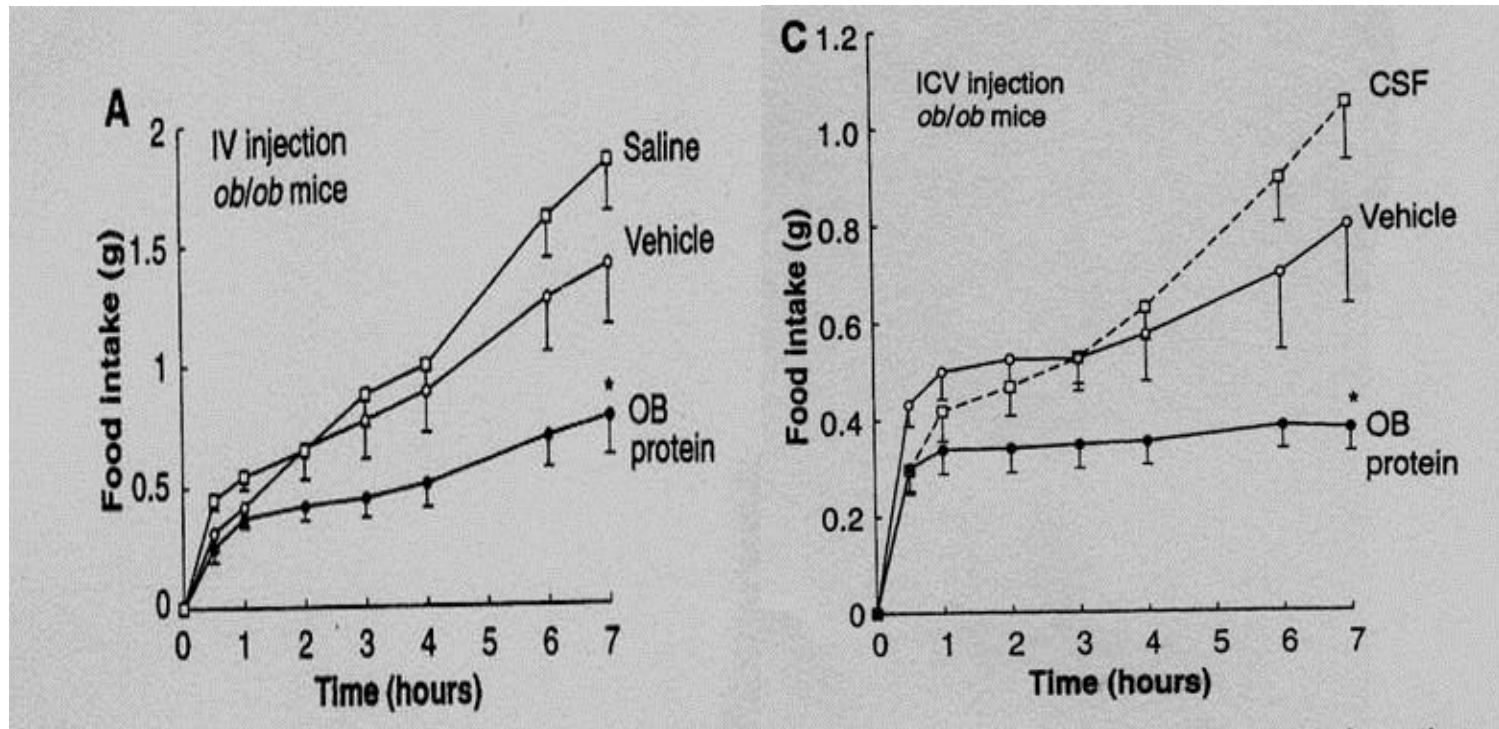
The ob/ob mice lack the lipostatic factor and cannot control food intake.

The db/db mice have the lipostatic factor but do not respond to it because of a problem in the hypothalamic satiety center.

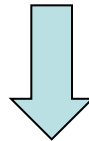
Coleman 1970



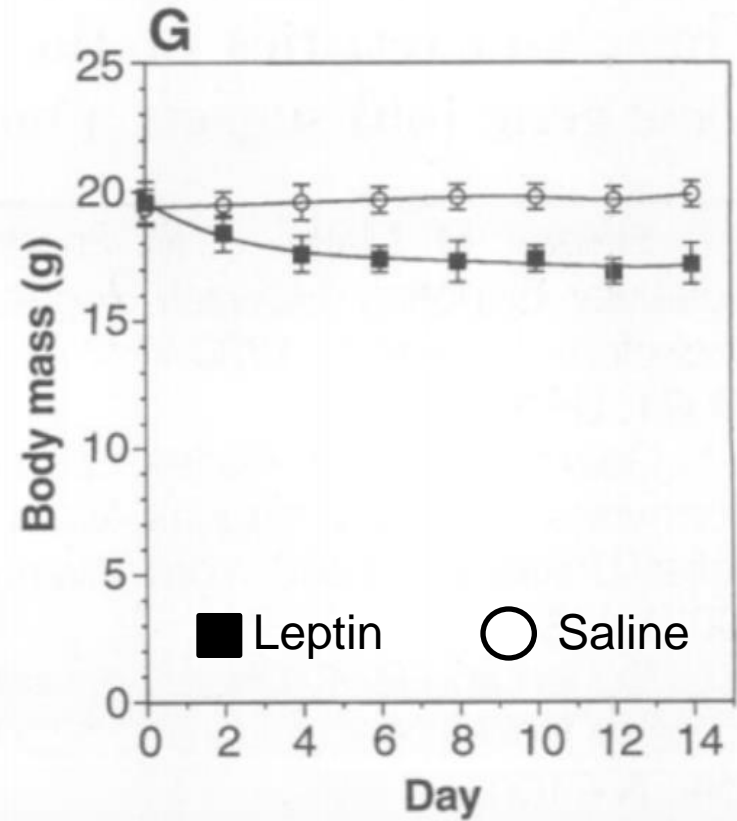
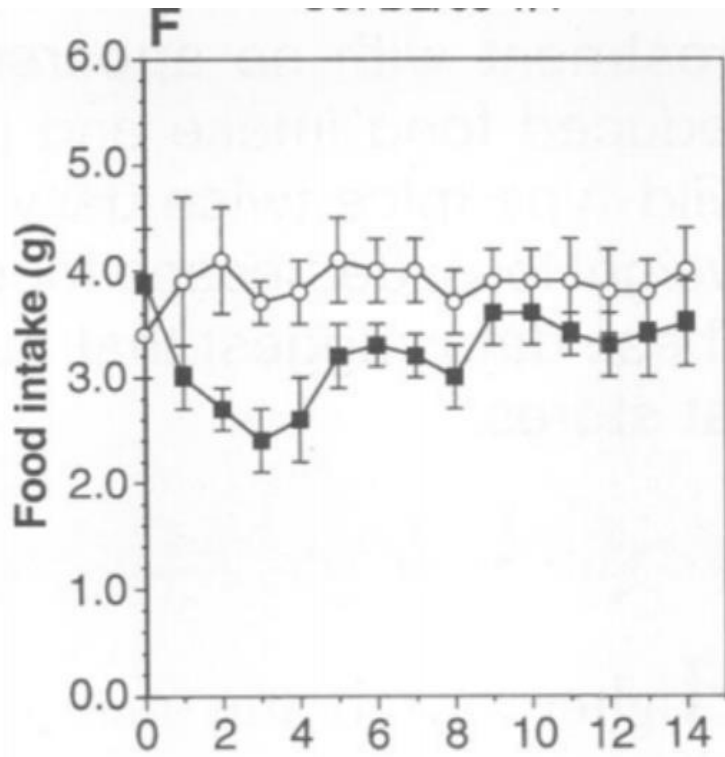
“leptin” from the Greek root leptos for “thin”



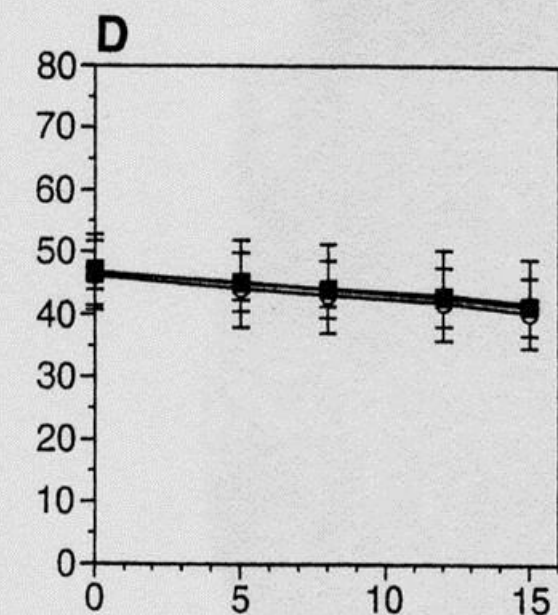
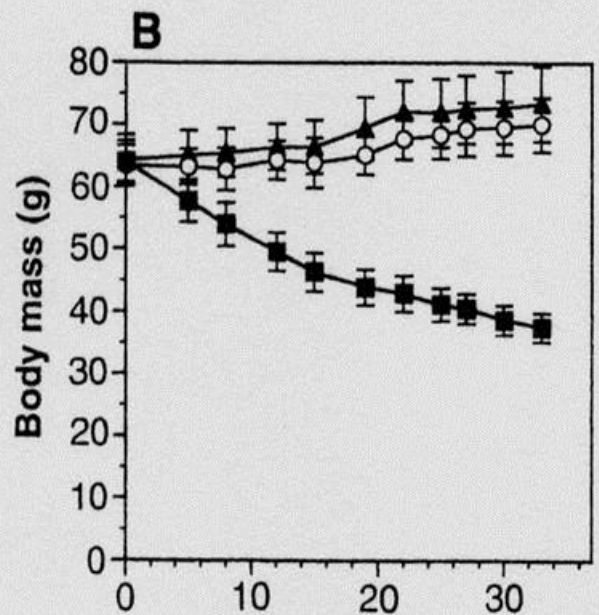
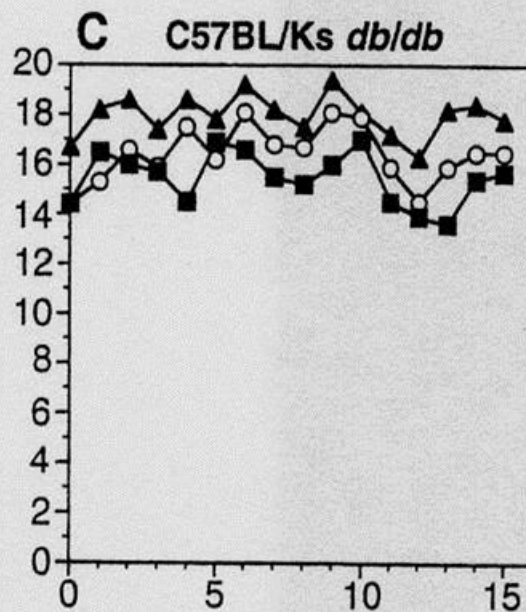
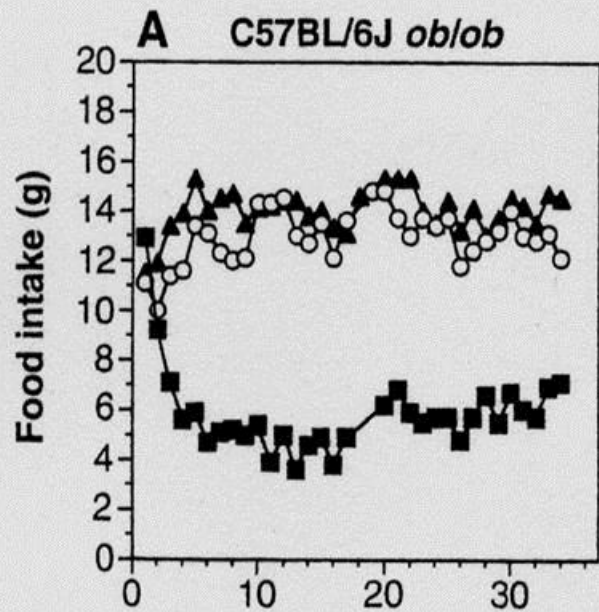
- One IV injection of leptin led to reduced food intake
- One ICV injection of leptin led to reduced food intake



- Leptin works at the level of the hypothalamus
- Leptin can cross the BBB



Daily IP injections of leptin led to reduced food intake and reduced body weight of wildtype mice



- 5µg leptin/day
- PBS
- ▲ No injection

Leptin had an affect on food consumption and body mass of *ob/ob* but had no effect on *db/db*

Congenital leptin deficiency is associated with severe early-onset obesity in humans

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A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction

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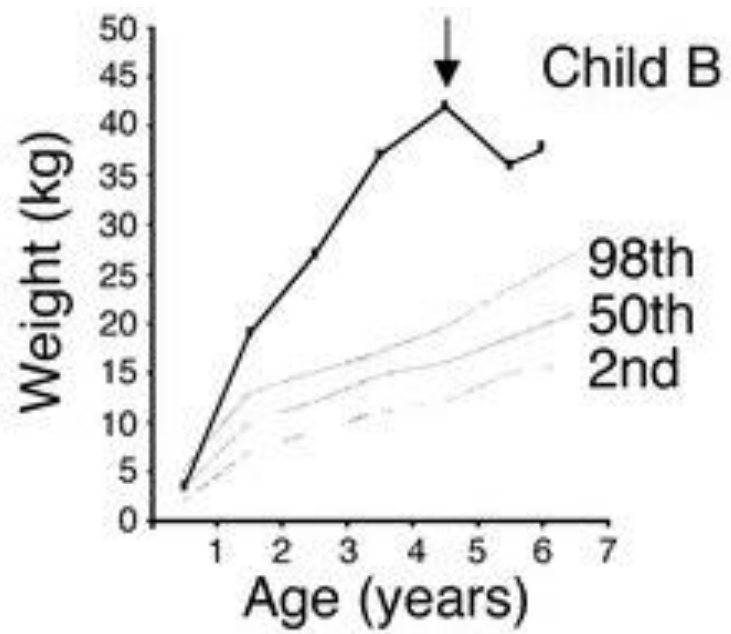
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Leptin deficiency

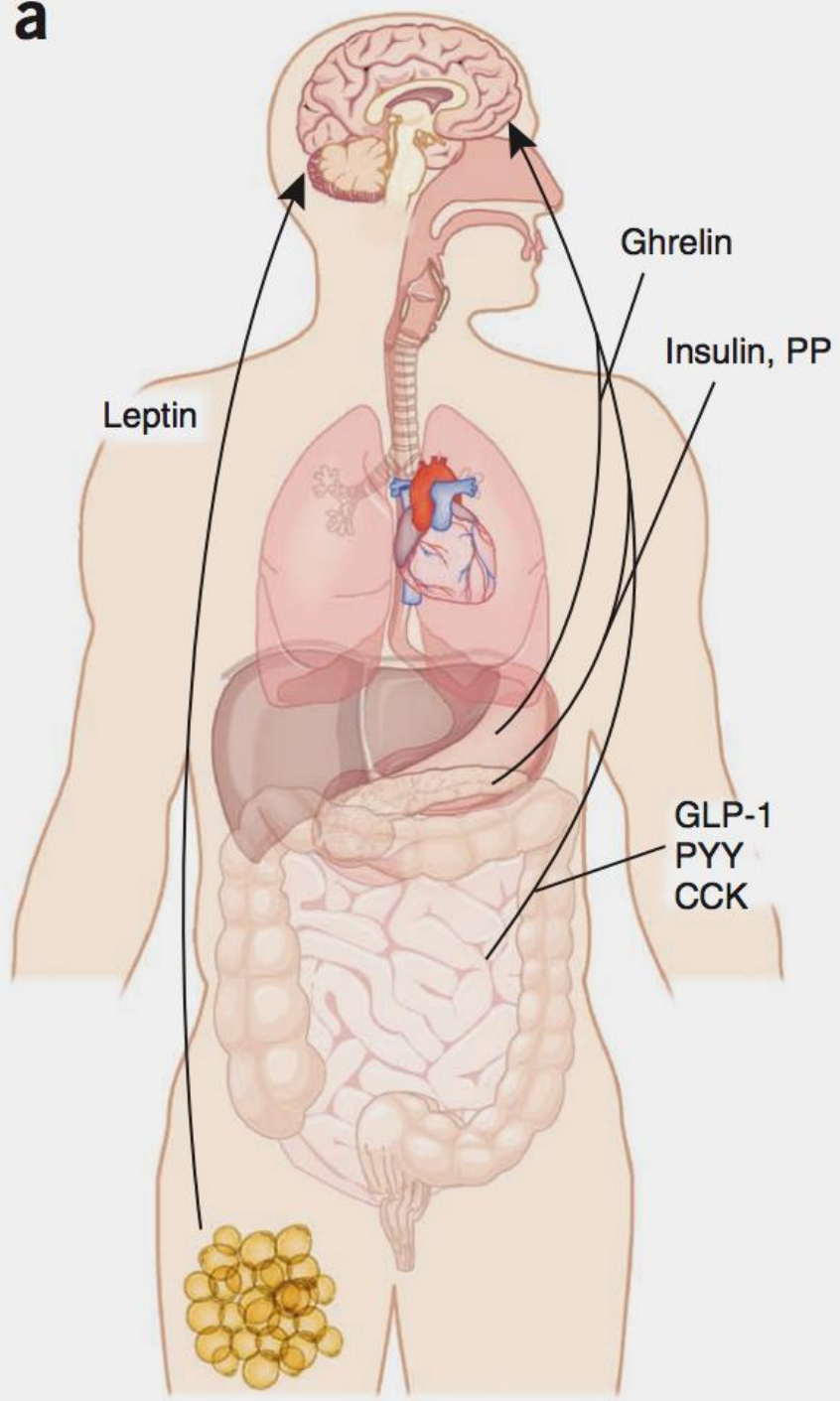


Clinical photographs of child B before and 24 months after Leptin therapy



Fig. 9 Leptin deficiency in humans responds to leptin treatment. A 3-year-old boy with congenital leptin deficiency with severe obesity (body weight 38 kg; BMI SD = 7.2) (left). On the right, the same patient, after four years of daily subcutaneous administration of recombinant leptin. Leptin treatment results in a dramatic decrease in adiposity (body weight 29 kg; BMI SD = 0.9) and normalization of all metabolic abnormalities including hyperinsulinaemia. Figure generously provided by Drs Sadaf Farooqi and Stephen O'Rahilly.

a



food intake up
temperature down
energy expenditure down
reproductive function down
parasympathetic activity up

food intake down
energy expenditure up
sympathetic activity up



leptin level falls

leptin level rises



weight loss

weight gain

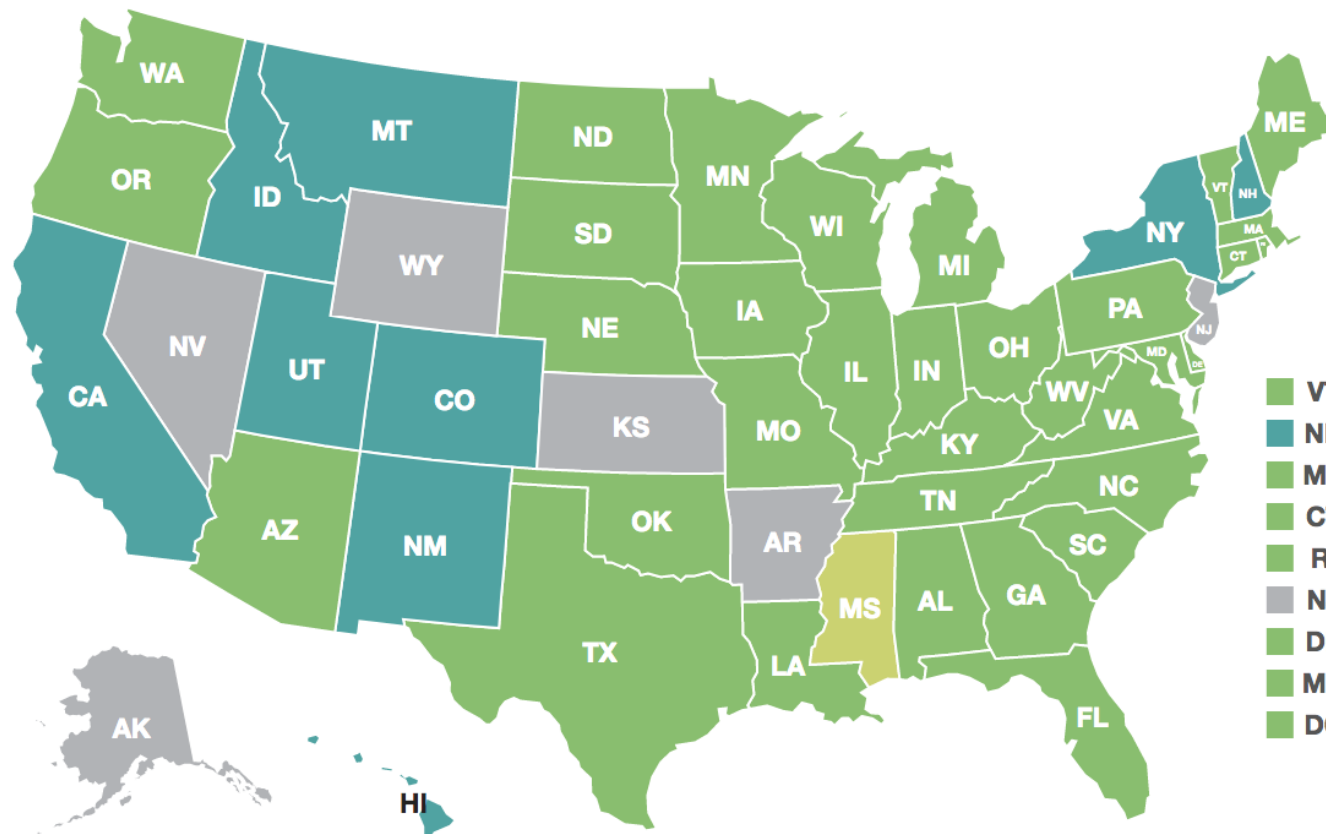


adipose tissue

Adult Obesity in the United States 1990

Percent of obese adults (Body Mass Index of 30+)

0 - 9.9% 10 - 14.9% 15 - 19.9% 20 - 24.9% 25 - 29.9% 30 - 34.9% 35%+



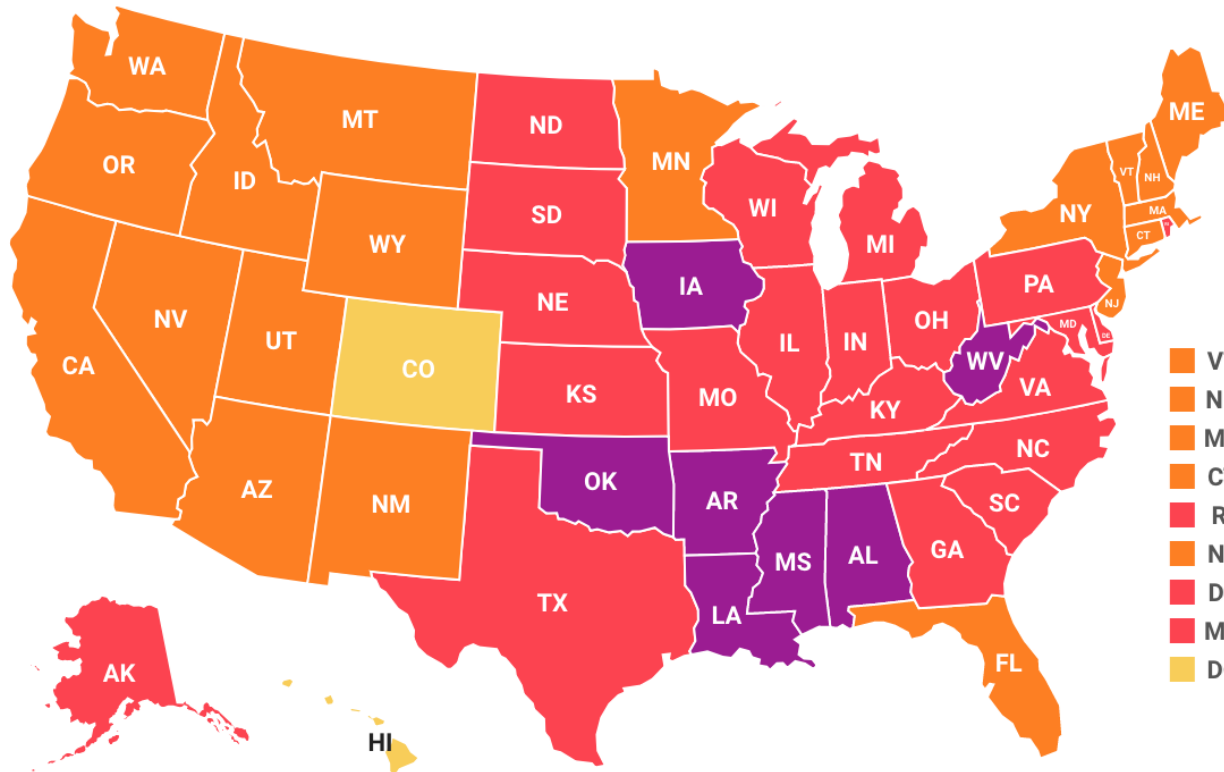
BMI:
Normal 18.5-25
Overweight 25-30
Obese > 30
Severely obese >35

- VT
- NH
- MA
- CT
- RI
- NJ
- DE
- MD
- DC

2017 Adult Obesity in the United States

Percent of obese adults (Body Mass Index of 30+)

0 - 9.9% 10 - 14.9% 15 - 19.9% 20 - 24.9% 25 - 29.9% 30 - 34.9% 35%+

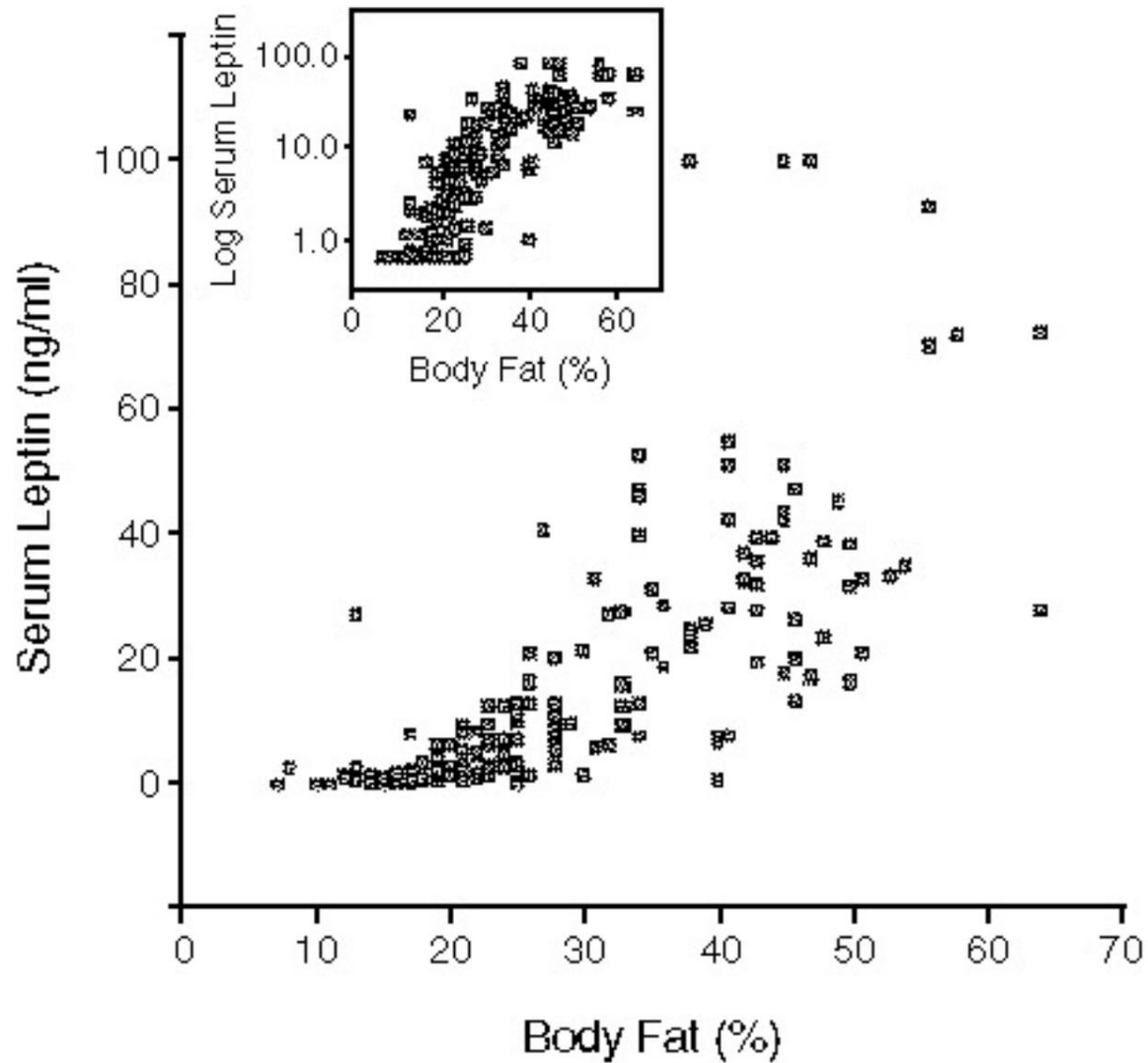


● All States ● West ● Midwest ● South ● Northeast

BMI:
Normal 18.5-25
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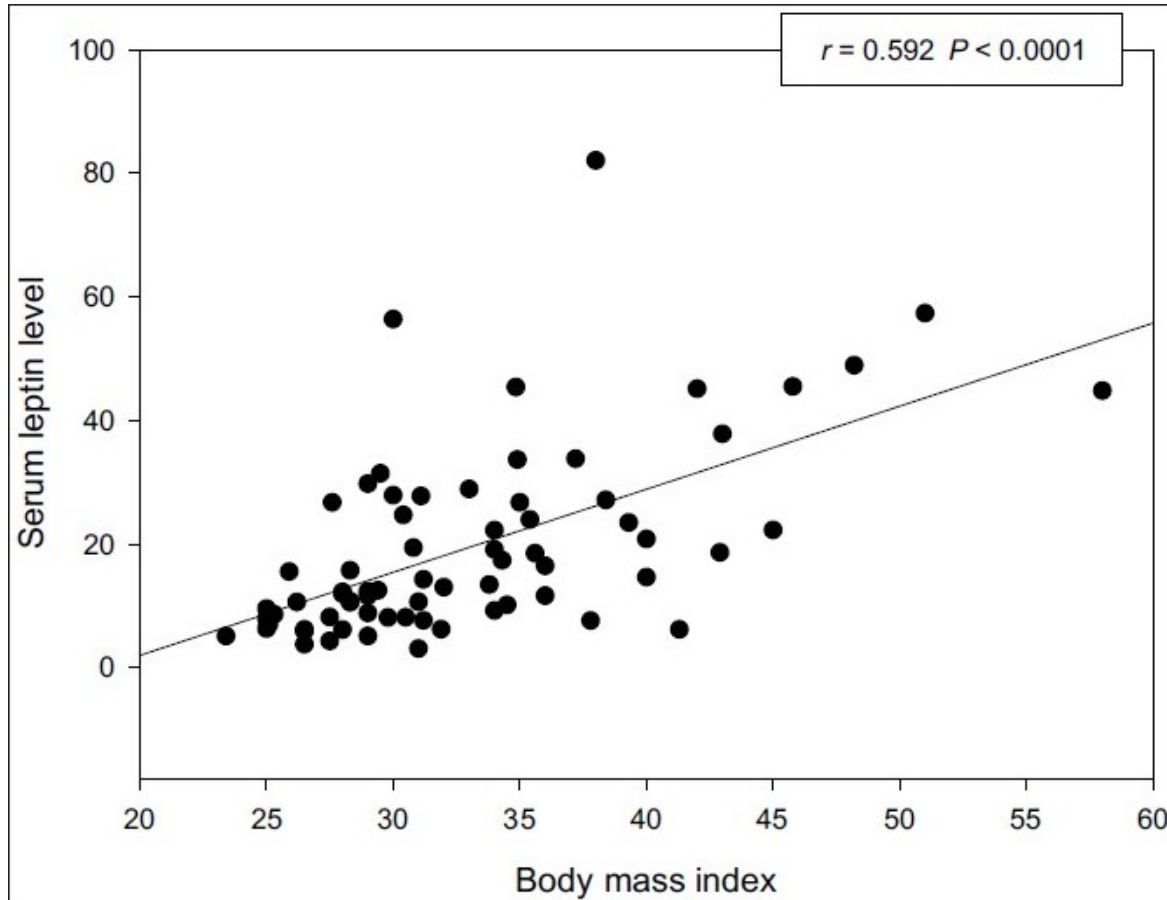
VT
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Blood Leptin concentration correlates with body weight in humans



What can you conclude from this graph?

Leptin resistance in obesity

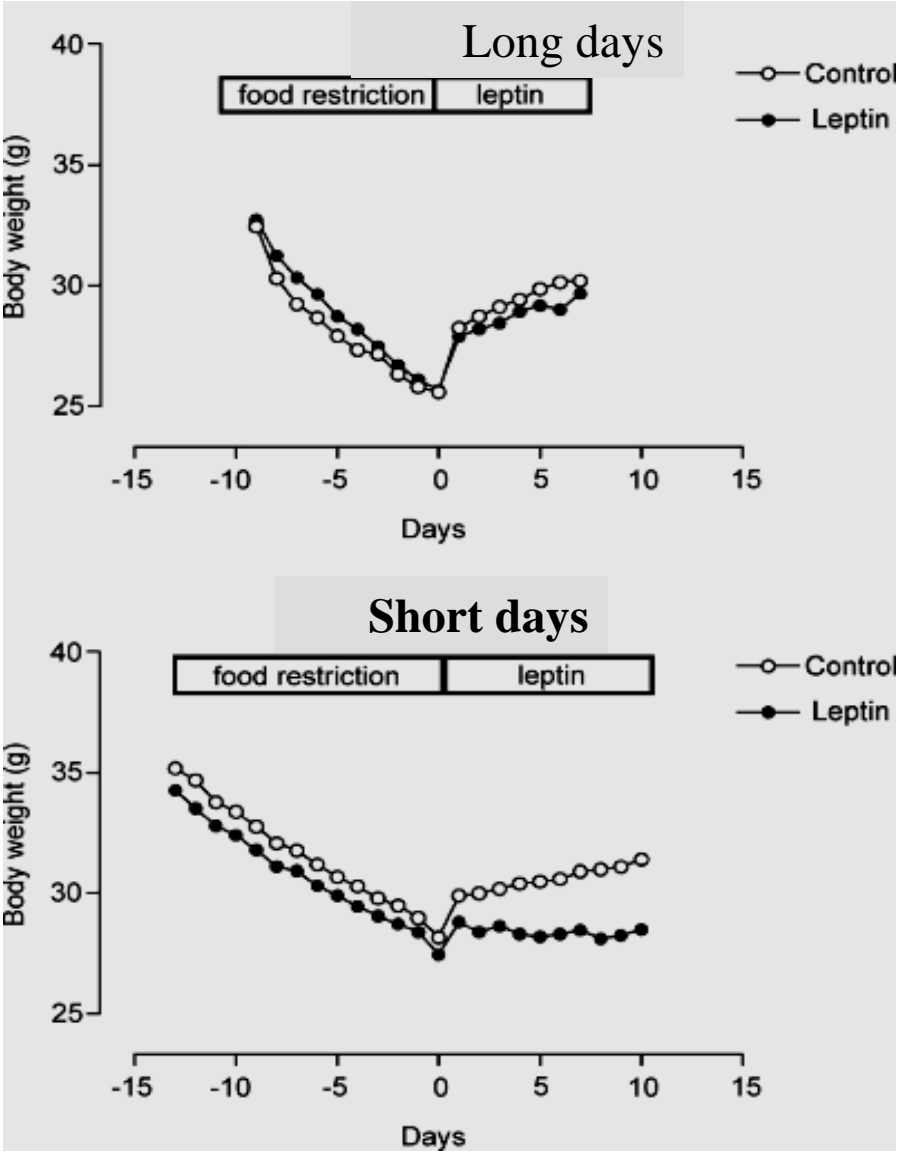


BMI > 30 is considered obese

Potential contributors to leptin resistance in obesity

- **Hyperleptinemia** - Chronic exposure to high levels of circulating leptin (hyperleptinemia) causes leptin resistance, presumably by over-activating negative feedback regulators.
- **Inflammation** Low-grade, chronic inflammation is closely associated with various metabolic disorders including obesity. High fat diet (HFD) feeding can promote inflammation in the hypothalamus.
- Hypothalamic **ER stress** is observed in HFD-fed mice. Pharmacological ER stress inducers impairs leptin signaling, whereas treatments with chemical ER chaperons relieve hypothalamic ER stress and decrease body weights in ob/ob mice.

Leptin resistance in humpsters under long days



a

What is happening in the hypothalamus?

