

Homeostasis and Mechanisms of Weight Regulation

Purpose

In this activity students will investigate how negative feedback mechanisms function to maintain homeostatic balance using a recently discovered system involved in body weight regulation as a model. This activity would be most appropriate for use in courses in anatomy and physiology or AP Biology.

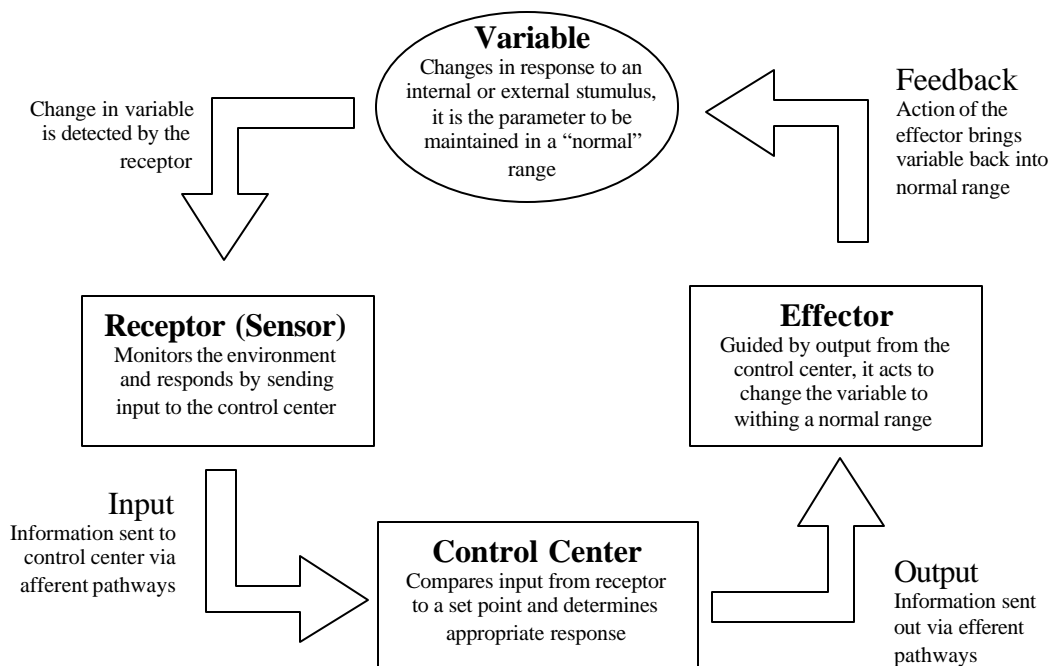
Objectives

By the end of this activity the student should be able to

- 1) Describe the main components of a negative feedback system.
- 2) Explain a current model of our understanding of how body weight is maintained.
- 3) Infer how mutations in key proteins can affect the weight regulation homeostatic mechanism.

Background

Homeostasis is the maintenance of a “steady state” within the body. How the body maintains homeostasis can be most easily described by focusing on a single physiological parameter such as body temperature or heart rate. In order to respond to changes in the internal or external environment, there must exist some type of detectors that can sense the levels of certain variables. These sensors then relay information on the status of the body to a control center, which compares the inputs to a pre-determined set point. The control center then sends output to an effector, which can then institute some type of response that will help to bring the parameter in question back within the desired range. A schematic of an idealized homeostatic system is illustrated below.



The most common control system encountered in everyday life is the one that is used to maintain a constant temperature within your home. The variable being controlled in this example is the temperature of the room. In the summertime, heat is constantly moving into your home from outside and the temperature inside begins to rise. The thermostat on the wall contains both the receptor (sensor) and the control center. The receptor constantly monitors the room temperature and relays this information to the control center. Inside, the control center is programmed to a certain upper set point, say 72°F. When the input from the sensor indicates that the room is above 72°F, the control center will throw a switch that sends an efferent electrical signal to the effector, the air conditioning unit. As the air conditioner runs, it removes heat from inside the house and pumps it outside, bringing down the temperature in the house. The sensor continues to send input to the control center and when the temperature drops below a lower set point, say 68°F, the output to the air conditioner is shut off. The system continues to cycle like this between cooling and not cooling, maintaining the room temperature in a range between 68° and 72°F.

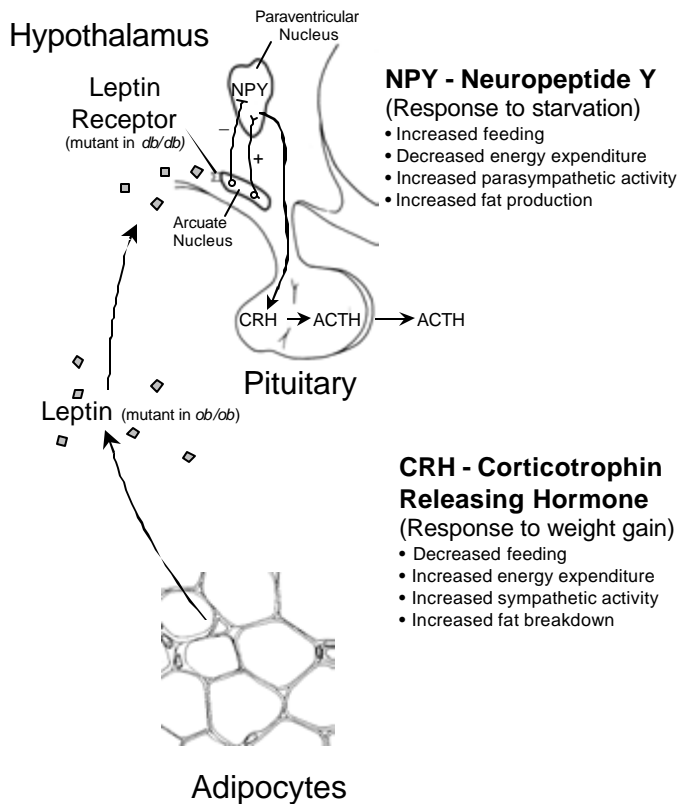
This particular type of control system is called a negative feedback system. The output of the system (in this case the cold air from the air conditioner) tends to shut off or decrease the initial stimulus (the high temperatures in the house). Most homeostatic control mechanisms in the body work by negative feedback. For example, the body's temperature is maintained around 37°C. If you get too warm, sensors in the hypothalamus of the brain will signal control centers that will produce sweating and vasodilation of the skin, both allowing heat to leave the body. This lowers body temperature, bringing it back to within normal range.

The amount of body fat carried is also under homeostatic control. While the mechanisms underlying the regulation of body weight are very complex, and not completely understood, a simplified model is described here. It has been recently discovered that adipose tissue produces and secretes a chemical messenger, a protein named leptin, that travels through the circulation to all parts of the body. It has been suggested that leptin is the signal that the body uses to determine the amount of body fat present. More fat tissue produces more leptin and less fat produces less leptin.

On the surface of cells in many of the major organs, including the brain, liver, and pancreas, lie receptors that are sensitive to the presence of leptin. In the brain, some of these receptors help to transport leptin across the blood-brain barrier. Once in the hypothalamus, the leptin binds to specialized forms of receptors on the surface of neurons in a region known as the arcuate nucleus. Once these receptors are bound with molecules of leptin, a cascade of events take place within these neurons.

One subset of neurons in the arcuate nucleus are stimulated to send excitatory signals to another region of the hypothalamus, the paraventricular nucleus, which has been shown to play an important role in hunger and satiety. Once stimulated in this manner, the neurons of the paraventricular nuclei will release corticotrophin releasing hormone (CRH) through direct projections to the posterior pituitary. This release of CRH will then cause the further release of another hormone, adrenocorticotrophic hormone (ACTH) into the general circulation. ACTH stimulates the adrenal cortex to release glucocorticoids, which in the body cause a mobilization of fats for energy metabolism. In addition, release of CRH by the hypothalamus also stimulates

the sympathetic nervous system, which results in increased metabolic rate and other catabolic processes.



A second subset of neurons in the arcuate nucleus appear to be inhibited by binding of leptin to its receptor. These neurons also have projections to the paraventricular nucleus, however they usually produce another protein, neuropeptide Y (NPY). NPY is widely distributed in the central nervous system, however when it is secreted in the paraventricular nucleus, NPY serves to support anabolic processes by increasing feeding, decreasing metabolic rate, increasing parasympathetic output, and stimulating the formation of adipose tissue. However, you should remember that these neurons are inhibited by the presence of leptin, which results in less NPY in the paraventricular nuclei, which blocks all of its downstream effects.

In summary, the presence high levels of leptin has at least two effects on the hypothalamus. The first is to stimulate the production of

CRH, which in turn speeds up metabolism and the breakdown of fat energy stores. On the other hand, leptin inhibits the output of NPY by the hypothalamus, which ultimately has the same overall effects as the CRH system. These two regulatory systems are summarized in the figure above.

The function of leptin was discovered through the study of two mouse mutants. In the 1950's, a mutation, *obese (ob)*, was discovered that caused mice to become morbidly overweight. Later, a second mutation, *diabetic (db)*, was also discovered in which the phenotype included excessive overeating and weight gain, similar to that seen in the *obese* mutant. It wasn't until the 1990s that the mechanisms underlying these mutations were discovered. The *ob* gene coded for an inactive form of the previously unknown protein, leptin. Later it was discovered that the *db* mice possessed a mutation in the leptin receptor, making the brain and other organs insensitive to the effects of leptin.

In 1973, Coleman performed experiments to investigate interactions between normal "wild type" mice and the *ob* and *db* mutants. In order to see how factors circulating in the blood affected these mice, he formed a parabiosis between various combinations of mice. In a parabiotic

experiment the abdominal cavities of two mice are surgically fused so that blood plasma may move from one animal to another. He produced three types of parabioses:

- 1) Between a mouse homozygous for the diabetic gene (*db/db*) and a wild type (+/+) lean mouse;
- 2) Between a (*db/db*) mouse and one homozygous for the obese gene (*ob/ob*); and
- 3) Between *ob/ob* and +/+. He then allowed the pairs of mice unlimited access to food and water and made observations of their body weight and measured a number of other parameters such as blood sugar level.

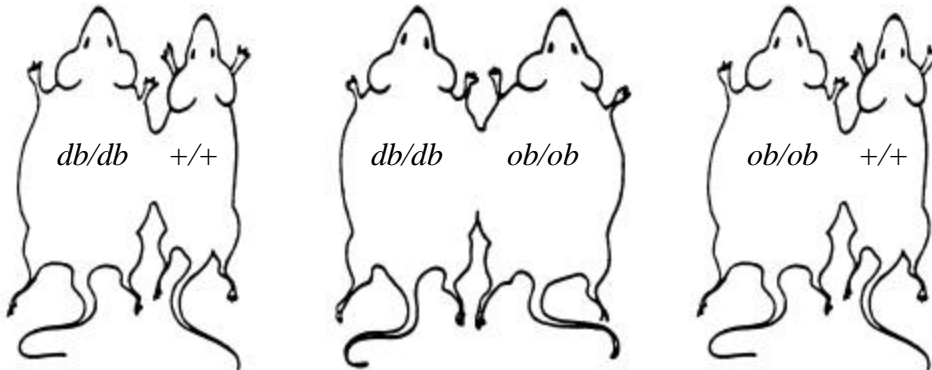


The parabiotic preparation.

Using what you know about leptin and the control system for fat deposition, predict what will happen to each parabiotic pair of mice. Possible outcomes are: maintain body weight, gain weight, lose weight to normal levels, and, stop feeding until starvation kills the mouse.

Remember that:

- 1) Leptin is produced by adipocytes: more fat = more circulating leptin.
- 2) When leptin binds to receptors in the hypothalamus it serves to increase metabolism and decrease fat stores.
- 3) *ob/ob* mice produce an inactive form of leptin; *db/db* mice produce a non-functional leptin receptor.



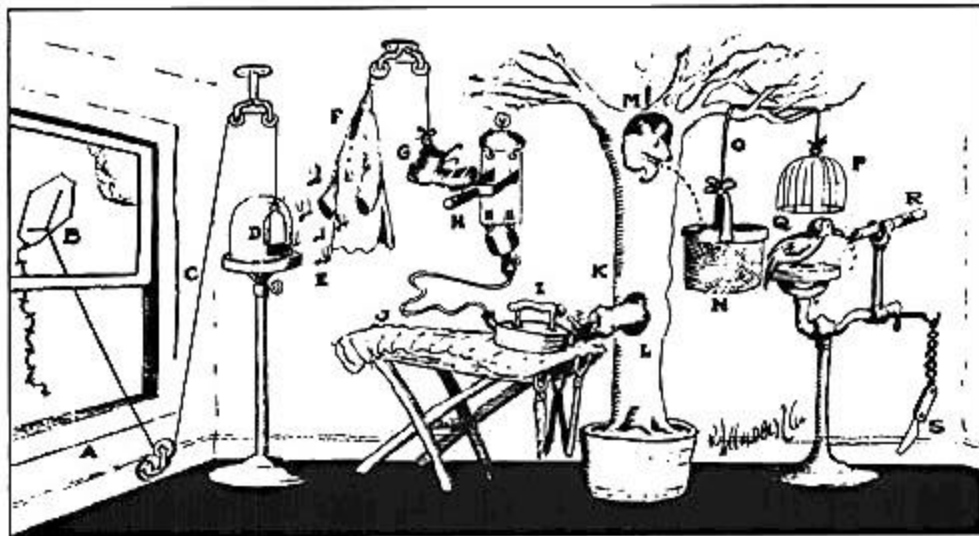
Questions

1. Is the leptin mechanism of weight regulation a negative or positive feedback system? How can you tell?
2. Which components of the leptin system represent:
 - a) the variable?
 - b) the receptor?
 - c) the control center?
 - d) the effector(s)?

3. Of what advantage is there in having more than one type of output from this system? In other words, why have outputs through both the CRH system and the NPY system?
4. Recently two cousins have been discovered who have a genetic defect similar to the *ob/ob* mutation in mice. For each of the following proposed treatments, give an expected outcome and reasoning for that outcome.
 - a) Daily injections of a leptin receptor blocker (antagonist) in the cerebrospinal fluid.
 - b) Daily intravenous injections of leptin.
 - c) Daily injections of NPY into the hypothalamus.
 - d) Daily intravenous injections of CRH.

Going Further

Design a “Rube Goldberg” model of a negative feedback homeostatic control mechanism and illustrate it on a piece of paper. (Rube Goldberg was a cartoonist known for inventing wild contraptions that performed everyday tasks. The board game “Mousetrap” was created in the Rube Goldberg style.) Your mechanism must include a sensor, control center, and an effector. Also, be sure you identify the variable being regulated.

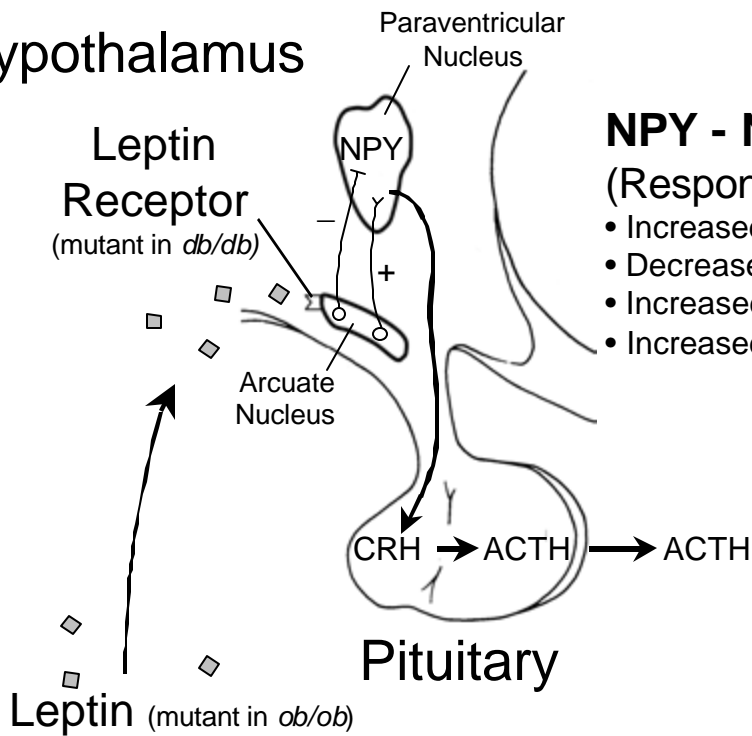


Pencil Sharpener RUBE GOLDBERG (tm) RGI 038

Rube Goldberg Pencil Sharpener

Open window (A) and fly kite (B). String (C) lifts small door (D) allowing moths (E) to escape and eat red flannel shirt (F). As weight of shirt becomes less, shoe (G) steps on switch (H) which heats electric iron (I) and burns hole in pants (J). Smoke (K) enters hole in tree (L), smoking out opossum (M) which jumps into basket (N), pulling rope (O) and lifting cage (P), allowing woodpecker (Q) to chew wood from pencil (R), exposing lead. Emergency knife (S) is always handy in case opossum or the woodpecker gets sick and can't work.

Hypothalamus



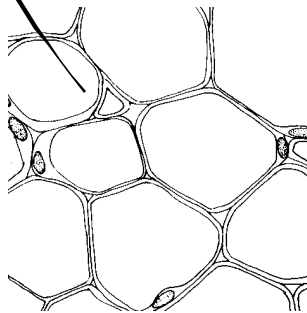
NPY - Neuropeptide Y (Response to starvation)

- Increased feeding
- Decreased energy expenditure
- Increased parasympathetic activity
- Increased fat production

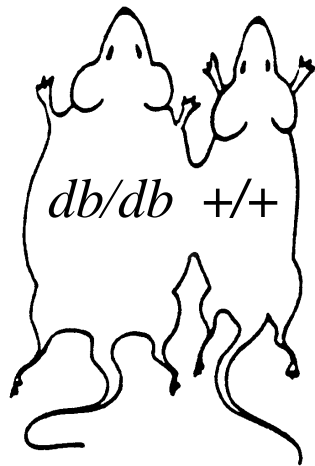
CRH - Corticotrophin Releasing Hormone (Response to weight gain)

- Decreased feeding
- Increased energy expenditure
- Increased sympathetic activity
- Increased fat breakdown

Leptin (mutant in *ob/ob*)

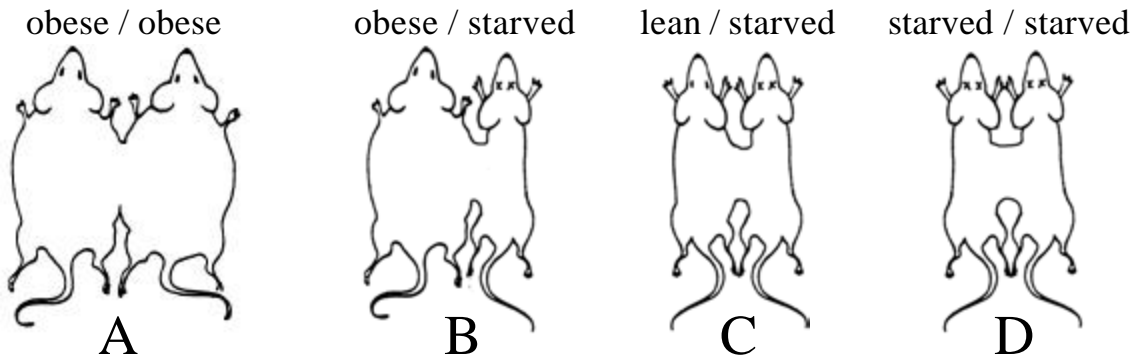


Adipocytes



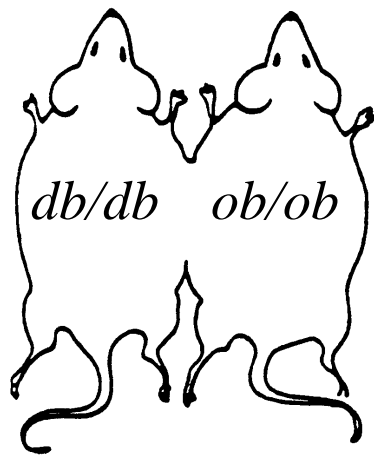
Case 1: Parabiosis
between *diabetic*
and *wild type* mice.

Predict the outcome



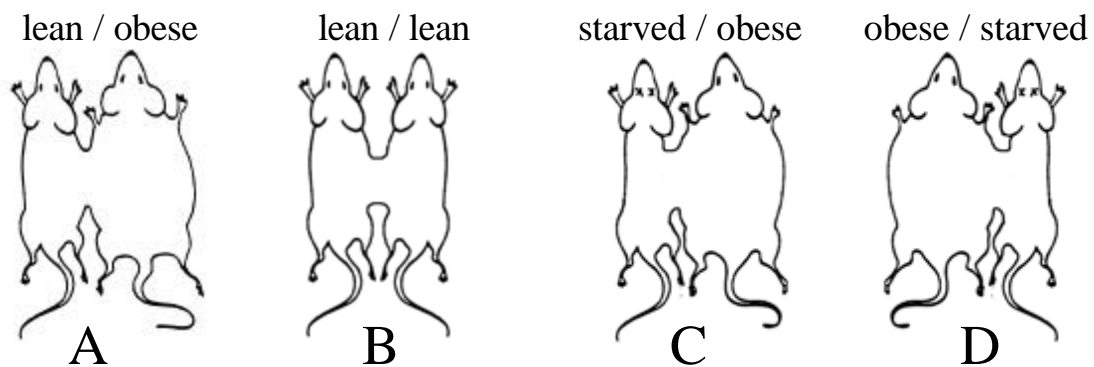
Rationale: The *diabetic* mouse has a defective leptin receptor and is unable to respond to the high levels of circulating leptin it produces and stays obese. The *wild type* mouse responds to the leptin produced by the diabetic partner by ceasing to eat and increasing metabolism. It loses weight until it dies from starvation.

Correct answer: B



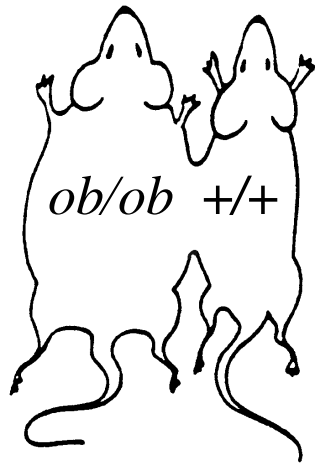
Case 2: Parabiosis between *diabetic* and *obese* mice.

Predict the outcome



Rationale: The *diabetic* mouse has a defective leptin receptor and is unable to respond to the high levels of circulating leptin it produces. It remains obese. The *obese* mouse responds to the leptin produced by the diabetic partner by ceasing to eat and increasing metabolism. It continues to lose weight until it dies from starvation.

Correct answer: D



Case 3: Parabiosis between *obese* and wild type mice.

Predict the outcome

lean / lean



B

obese / starved



A

lean / starved



C

obese / obese



D

Rationale: The *wild type* mouse maintains normal homeostasis, unaffected by the high levels of defective leptin produced by its *obese* mate. The *obese* mouse responds to the normal leptin levels produced by the *wild type* mouse and loses weight until it reaches normal levels.

Correct answer: A