Internal Regulation II: Energy
Biologically, what is necessary for life is a coordinated set of chemical reactions. These reactions take place in water at a rate dependent on the temperature of the solution, concentration of the solutes and availability of energy.

Homeostasis refers to biological processes that keep body variables within a fixed range. If the range is very narrow, then it is referred to as a set point.

The process of homeostasis includes:
- sensory transduction of a variable and signaling changes from the optimal range
- integrated response (visceromotor, humoral and somatic) to restore parameter back to optimal (called negative feedback)

The hypothalamus plays a key role in the regulation of body temperature, fluid balance, and energy balance.
Hypothalamus and Homeostasis

The hypothalamus orchestrates a (three-part) response to maintain the homeostasis of body parameters. The response includes:

- **autonomic** (visceromotor): fast physiological adjusting the sympathetic/parasympathetic autonomic nervous system (ANS)
- **endocrine** (humoral): slow physiological releasing hormones
- **somatic** (behavioral): motivating appropriate behaviors by the somatic motor system

The **paraventricular nucleus (PVN)** initiates the autonomic and endocrine responses:

- dorsal and ventral parvocellular cells \(\rightarrow\) ANS
- medial parvocellular cells release hormones to control hormones from the anterior pituitary;
- magnocellular cells release directly hormones from the posterior pituitary

The **lateral hypothalamic area (LHA)** motivates the somatic motor response via release of orexin and melanin-concentrating hormones in dorsolateral prefrontal cortex.
The gastrointestinal tract (GIT) is a part of the physiological system involved in the regulation of the body’s energy homeostasis.

The GIT is an organ system which takes in food (mouth), digests it (mouth, stomach, and small intestines) to extract and absorb energy and nutrients (small and large intestines), and expels the remaining waste as feces (rectum).

The digestive system can influence food intake in multiple ways:

- lactose intolerance
- conditioned taste aversion
The brain’s need for energy (glucose) is urgent: a lack for even a few minutes will lead to loss of consciousness and death.

The body’s energy stores are replenished following food intake. During the prandial state, glucose is stored (via anabolism) in the form of two macromolecules: glycogen (in the liver and skeletal muscles) and triglycerides (in fat). During the fasting state, stored molecules are broken down (via catabolism) to provide nutrients.

Homeostatic mechanisms aim to reach an equilibrium between energy intake and energy expenditure. Body weight is a settling point (a balance between hunger and satiety factors) not a set point.

Homeostatic (long- and short-term) and hedonic mechanisms regulate energy reserves and feeding.
Body weight is usually very stable in the long-term. Weight lost during a period of starvation is gained rapidly when food is available. Similarly, if an animal is force fed, it will gain weight, but the weight is lost if the animal can regulate its own food intake.

→ Lipostatic hypothesis: the brain monitors the level of body fat and “defends” this source against perturbation. Thus, long-term regulation of body weight is asymmetric (more sensitive to weight loss than weight gain).

Evidence suggests that fat cells release the hormone leptin to communicate the level of fat to the brain. In particular, mice lacking both copies of the *ob* gene (which codes for leptin) are obese, whereas deficient mice which receive daily doses of leptin are normal in size.

Leptin deficiency is rare in humans; rather obesity may be caused in part by decreased penetration through the blood-brain barrier; reduced receptors; altered CNS response.
Short-Term Regulation

In addition to the long-term regulation of feeding behavior by leptin, the motivation to eat depends on short-term factors such as the length of time since the last meal and how much was eaten.

Hunger/satiety is regulated by a variety of short-term factors including signals from the stomach, intestines and blood.

Stomach:
- hormone ghrelin (hunger)
- distention (vagus nerve) (satiety)

Intestines:
- hormone cholecystokinin CCK (satiety)
  (also closes the exit of the stomach causing its distention → activation of the vagus nerve)

Blood:
- hormone insulin (pancreas)
  low = hunger; high = satiety
Studies show that bilateral lesions of the hypothalamus have large effects on feeding behavior and adiposity.

Lateral hypothalamic syndrome: lesions here cause severely reduced appetite and reduced fat stores

Ventromedial hypothalamic syndrome: lesions (in the arcuate nucleus) cause severe overeating and weight gain

Energy needs are sensed by the arcuate nucleus, and changes are effected by the paraventricular nucleus and lateral hypothalamic area.
The arcuate nucleus (or infundibulum) of the hypothalamus is considered to be the “master area” (sensor) for control of appetite.

It has two sets of neurons: one set sensitive to hunger signals (purple) and one set sensitive to satiety signals (green).

When activated, hunger-sensitive neurons release AgRP and NPY onto their targets (PVN and LHA), whereas satiety-sensitive neurons release POMC and CART into the same targets (with opposite effects).
Many factors influence appetite including:

- **hunger**: low leptin, low insulin, low CCK, low gastric tension (via activity in the nucleus solitarius NS in the medulla) and high ghrelin
- **satiety**: high leptin, high CCK, high insulin and high gastric tension.

Hunger/satiety produces the following effects:

- **autonomic** (via dorsal and ventral PVN) activate parasympathetic or sympathetic nervous systems
- **endocrine** (via medial parvocellular PVN) decrease/increase release of thyroxine to affect metabolic rate
- **somatic** (via LHA) stimulate/suppress feeding via orexin (to initiate meal) and MCH (prolong feeding)
Hedonic Regulation of Feeding

Food is consumed in order to maintain energy balance at homeostatic levels. In addition, palatable food is also consumed for its desirable “hedonic” properties independent of energy status.

Certain foods, particularly those rich in sugars and fat, are potent rewards that promote eating (even in the absence of an energetic requirement). In evolutionary terms, this property was advantageous because it ensured that food was eaten when available.

Hedonic hunger incorporates motivational (reward) and emotional influences on eating. Evidence suggests that dopamine (ventral tegmental area) and serotonin (Raphe nucleus) modulate, respectively, these hedonic effects of food.
The brain contains two dopamine systems that project from the mesencephalon to the telencephalon.

- **nigrostriatal pathway (green):** substantia nigra to the striatum (motor selection)
- **mesocorticolimbic pathway (red):** ventral tegmental area (VTA) to cortex and limbic sites, including the nucleus accumbens (NA). The VTA to NA projection is the “reward” circuit (and site of action of addictive drugs).

The VTA is activated (in part) by the lateral hypothalamic area, hunger signals, and consideration by the dorsolateral prefrontal cortex of behaviors that previously elicited positive outcomes (e.g., memory of sugar influx following eating of a cookie). In turn, the VTA projects indirectly back to the dorsolateral prefrontal cortex. Thus, the VTA can incite feeding behavior if the body does or does not have energy needs.
Mood and food are connected (e.g., grouchy on a diet; happy eating a cookie).

Studies indicate that the neurotransmitter serotonin is involved in regulating mood. Serotonin-containing neurons are located in the Raphe nuclei of the brainstem, and their axons project to many structures involved in expressing emotion including the amygdala.

Serotonin is derived from the amino acid tryptophan, which must be consumed. It is found in proteins; however, tryptophan levels in the brain vary with the amount of carbohydrates in the diet (high levels $\rightarrow$ high insulin $\rightarrow$ more tryptophan crosses the blood brain barrier).

Serotonin promotes its own synthesis ... that is, low/high levels act as hunger/satiety signals in the arcuate nucleus.
Obesity

Obesity is a medical condition in which excess body fat has accumulated, with adverse health effects (e.g., heart disease and diabetes).

It is often caused by a mix of excessive food intake, lack of physical activity, and genetic susceptibility.

Dieting and exercising are the main treatments. If these do not work, then weight-loss drugs (e.g., serotonin or insulin agonists) or surgery may be effective.
Common eating disorders include anorexia nervosa and bulimia nervosa.

- Anorexia nervosa is a condition in which people refuse to eat or fear to eat as much as they need.
- Bulimia nervosa is characterized by binge eating (a large amount of food in a short amount of time) followed by purging (e.g., vomiting).

Risk factors for these diseases include psychological stress, cultural pressure to attain a certain body type, and genetic predisposition.

The study of genes related to eating disorders is in its early stages. Various related genes have been shown to disrupt the hedonic mechanisms that regulate feeding.