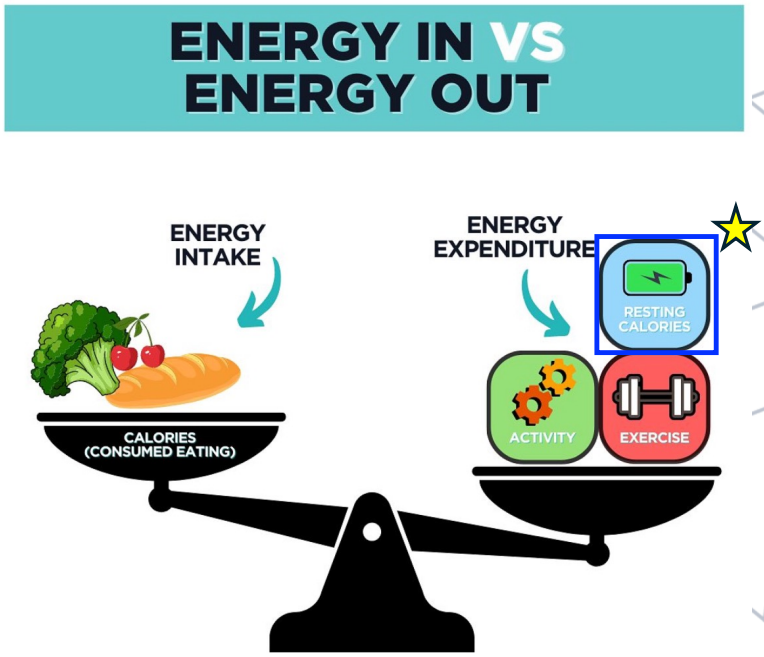
BIOC 385: M09.T03-Miesfeld

Assigned Reading: *Biochemistry* Chapter 22.2ab

Control of Energy Balance by Hormone Signaling

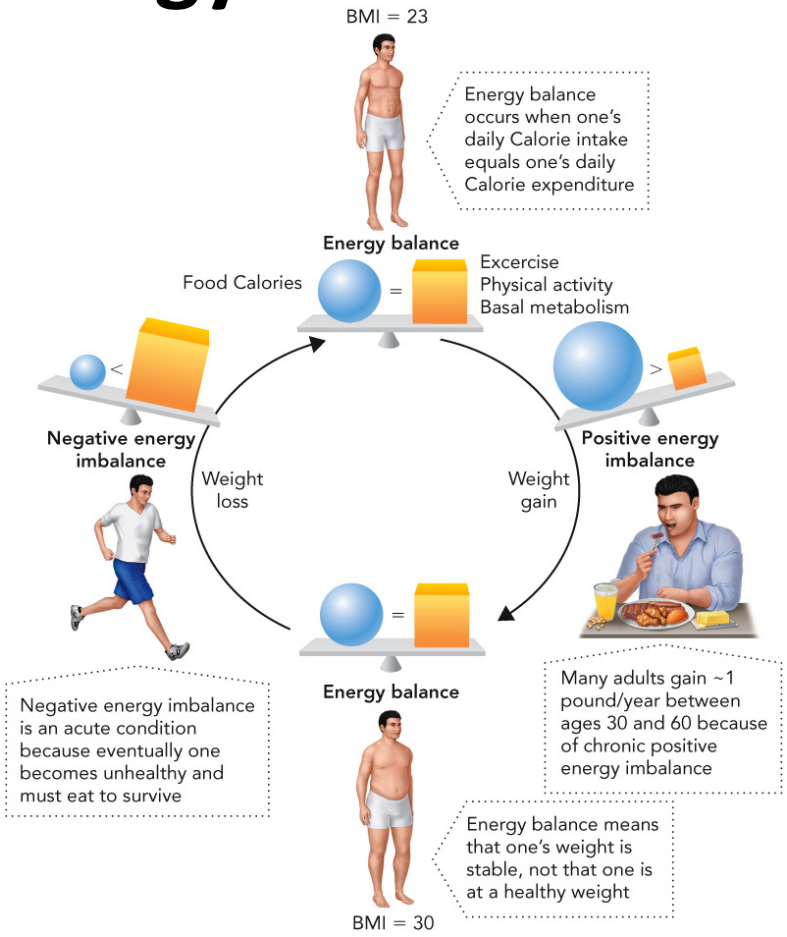
The Big Picture

- Energy balance is maintained when daily Caloric intake equals energy expenditure, with imbalances contributing to obesity, insulin resistance, and type 2 diabetes.
- Understanding genetic, environmental, and hormonal controls of energy balance provides insight into disease mechanisms and therapeutic strategies.



Positive and Negative Energy Balance

- Energy balance is achieved when dietary Calories consumed equal Calories expended; imbalance occurs if intake exceeds or falls below expenditure.
- Adults typically require 1500–2000 Calories/day, with an optimal intake ratio of 2:1:1 for carbohydrate:protein:fat, ensuring stable weight if fully utilized.



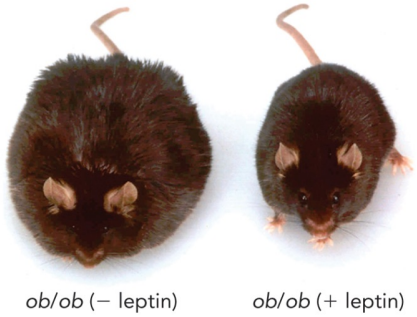
The Thrifty Gene Hypothesis

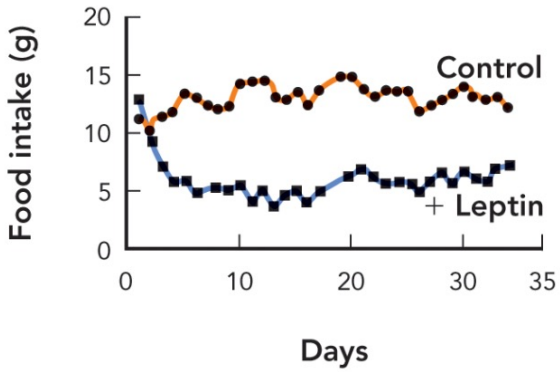
- The thrifty gene hypothesis suggests human evolution favored energy storage genes for survival during famine, but in modern societies, these variants promote obesity.
- High-Calorie diets combined with low physical activity convert ancient survival genes into disease risk factors, linking obesity and diabetes to genetic predisposition.

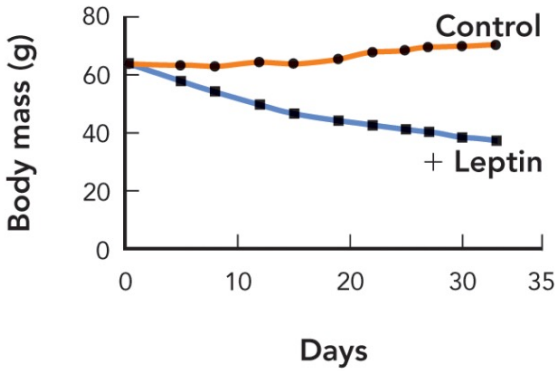
Figure 19.22

Leptin Hormone Controls a Metabolic Set Point

- Leptin injections in *ob/ob* mice reduce food intake, body weight, and serum glucose and insulin, demonstrating its role in regulating energy balance.







- Leptin injections in *ob/ob* mice reduce food intake, body weight, and serum glucose and insulin, demonstrating its role in regulating energy balance.

Physiological Effects of Leptin Hormone

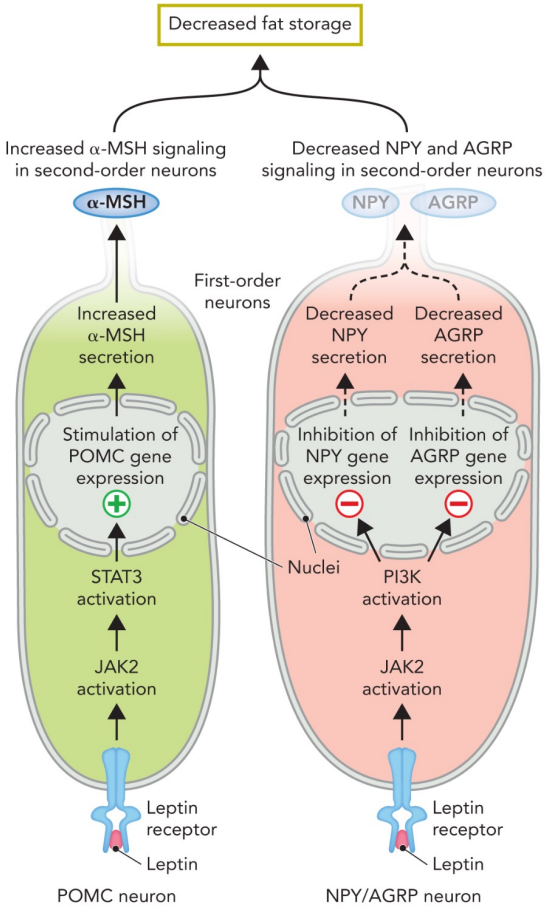
- Wild-type mice produce leptin and have normal receptor signaling, while *ob/ob* mice lack leptin and *db/db* mice lack receptor activity; results are obesity and diabetes.
- These models reveal how deficiencies in leptin signaling elevate glucose and insulin, establishing leptin as a critical regulator of appetite and metabolism.

Genotype	Leptin production	Leptin receptor	Body weight (g)	Serum glucose (mg/dL)	Serum insulin (ng/mL)	Serum leptin (ng/mL)
Wild type (+/+)	Yes	Yes	23.9	209.4	2.4	2.0
OB (*ob*/*ob*)	No	Yes	43.5	362.9	10.3	ND
DB (*db*/*db*)	Yes	No	41.4	489.9	21.3	73.1

Note: The symbol "+" refers to a normal copy of the genes encoding leptin (*ob*) and the leptin receptor (*db*). ND = not detected.

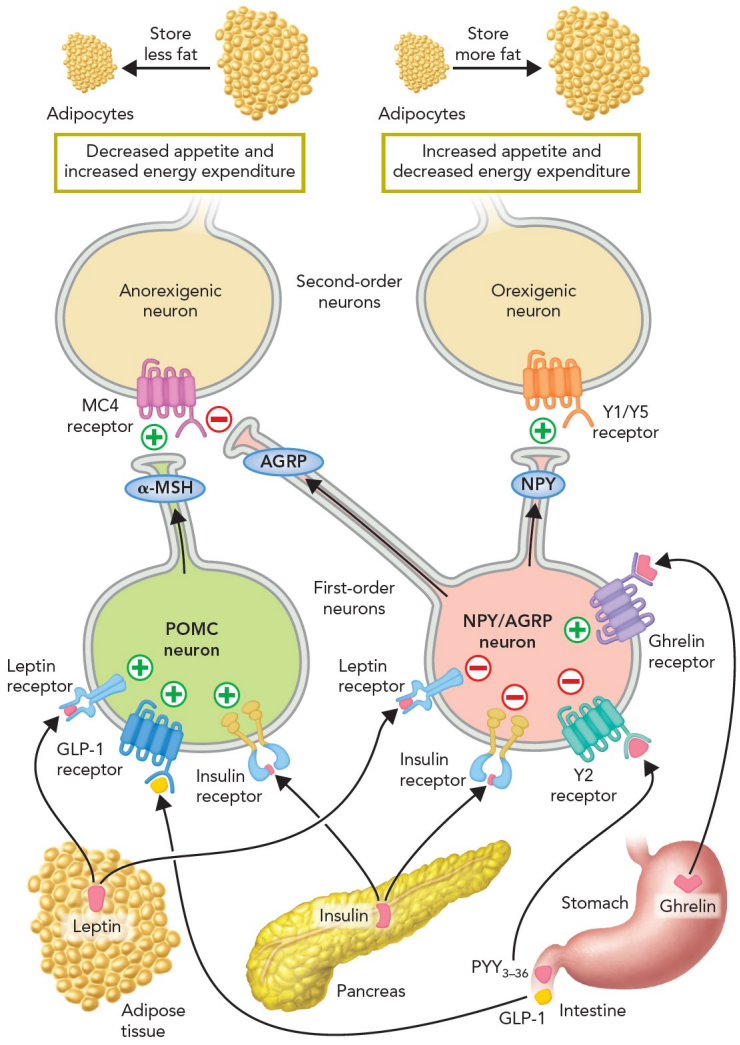
Leptin Signaling Pathways in the Brain

- In POMC neurons, leptin activates JAK2–STAT3 signaling, increasing α-MSH secretion and stimulating anorexigenic pathways to reduce fat storage.
- In NPY/AGRP neurons, leptin suppresses orexigenic signaling via PI3K, decreasing NPY and AGRP expression and further limiting fat storage.



Control of Appetite and Energy Expenditure

- α-MSH secreted by POMC neurons activates MC4 receptors on anorexigenic neurons, decreasing appetite and increasing energy expenditure.
- NPY and AGRP from NPY/AGRP neurons activate orexigenic neurons or block MC4 signaling, increasing appetite and fat storage unless inhibited by leptin.



Hormonal Modulation of Neuronal Circuits

- Similar to leptin, insulin also activates POMC neurons, leading to increased secretion of α-MSH and inhibits NPY/AGRP neurons to decrease secretion of the NPY and AGRP leading to decreases appetite and increases energy expenditure.

Peptide hormone	First-order neuron binding	Effect in first-order neurons	Effect in second-order neurons	Effect on energy balance
Leptin	POMC	Increased α-MSH secretion	Increased anorexigenic signaling	Store less fat
Leptin	NPY/AGRP	Decreased AGRP and NPY secretion	Decreased orexigenic signaling	Store less fat
Insulin	POMC	Increased α-MSH secretion	Increased anorexigenic signaling	Store less fat
Insulin	NPY/AGRP	Decreased AGRP and NPY secretion	Decreased orexigenic signaling	Store less fat

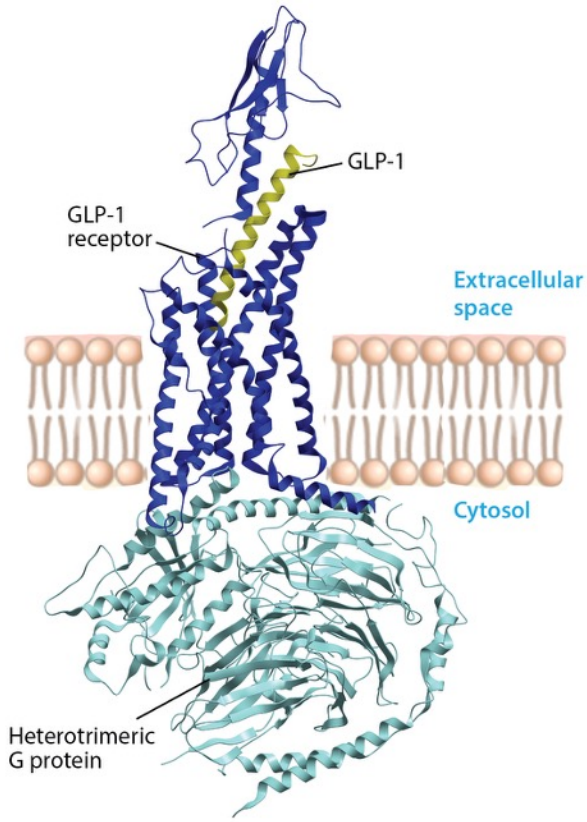
Hormonal Modulation of Neuronal Circuits

- GLP-1, and PYY3–36 stimulate anorexigenic pathways and inhibit orexigenic pathways; ghrelin opposes these signals by stimulating NPY/AGRP neurons, increasing appetite and promoting fat storage, especially between meals.

Peptide hormone	First-order neuron binding	Effect in first-order neurons	Effect in second-order neurons	Effect on energy balance
PYY3–36	NPY/AGRP	Decreased AGRP and NPY secretion	Decreased orexigenic signaling	Store less fat
Ghrelin	NPY/AGRP	Increased AGRP and NPY secretion	Increased orexigenic signaling	Store more fat
GLP-1	POMC	Increased α-MSH secretion	Increased anorexigenic signaling	Store less fat

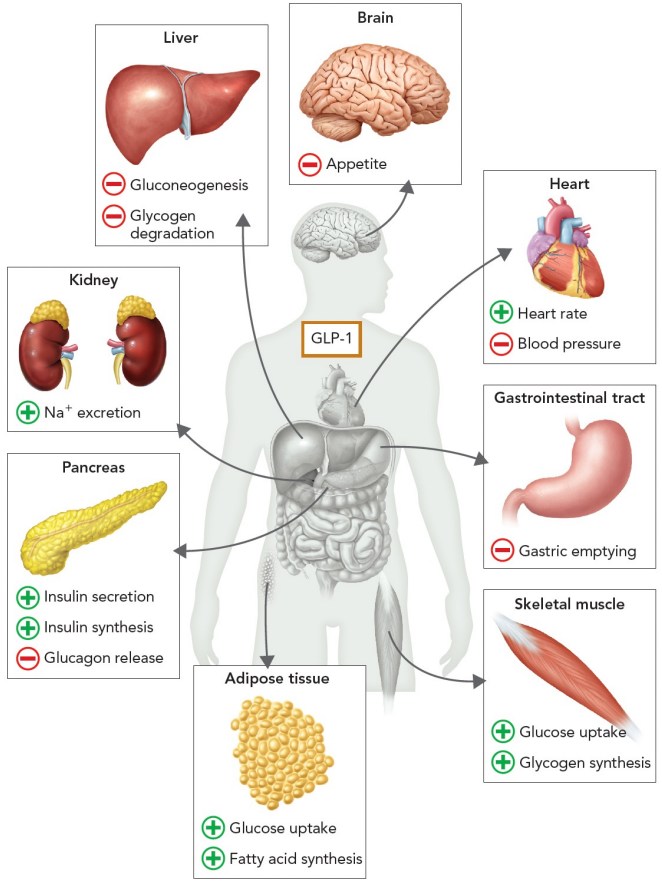
Structure of the GLP-1 Receptor Protein

- GLP-1, derived from proglucagon, binds to receptors on POMC neurons to increase α-MSH secretion and anorexigenic signaling, decreasing appetite.
- The GLP-1 receptor is a G protein–coupled receptor with extracellular GLP-1 binding and cytosolic G protein signaling, linking gut signals to energy balance.



GLP-1 Regulation of Metabolic Signaling

- GLP-1 receptor signaling increases insulin sensitivity, lowers blood glucose, reduces appetite, and slows gastric emptying to prolong satiety.
- GLP-1 receptor agonists such as semaglutide mimic these effects clinically, providing therapeutic benefit in obesity and type 2 diabetes.



Key Concepts to Guide Your Learning

- The thrifty gene hypothesis states that humans contain metabolic gene variants that provide protection against famine by maximizing fat storage when food is available.
- Leptin is an adipokine hormone synthesized in adipose tissue at levels proportional to the amount of stored fat and activates signal transduction in the hypothalamus leading to decreases appetite and increased energy to reduce the amount of stored fat.
- Leptin and insulin bind to first-order POMC and NPY/AGRP neurons that produce neuropeptides (α-MSH,NPY, AGRP) that stimulate anorexigenic neurons (eat less, metabolize more) and inhibit orexigenic neurons (eat more, metabolize less.
- Ghrelin is synthesized in the stomach and signals to the brain that it is time to eat, whereas $PYY_{3–36}$ is synthesized in the colon and signals that it is time to stop eating.
- Glucagon-like peptide 1 (GLP-1) is synthesized in the intestine and binds to GLP-1 receptors in POMC neurons mimicking the effect of leptin and insulin by activating anorexigenic neurons leading to decreased appetite and increased energy expenditure.