23 Hormonal Regulation and Integration of Mammalian Metabolism

P1 Principle 1 (1 of 4)

The tissues in a mammal are connected by a neurosecretory system that coordinates their activities. Mammals use chemically diverse hormones in a highly specific and multidirectional signaling system, connecting the tissues with each other and with the central nervous system.

P2 Principle 2 (1 of 3)

Among the tissues and organs of an animal, there is a striking division of labor. The specialized role of each organ is reflected in its metabolic activities and capabilities. The circulatory system connects all of the tissues by carrying hormonal signals and metabolites between and among them.

P3 Principle 3 (1 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

P4 Principle 4 (1 of 4)

Maintaining an optimal body mass is an important priority in the adult mammal. Body mass is a function of dietary intake, physical activity, and the choice of metabolic fuel, all of which are subject to hormonal regulation. Hormonal signals between the brain, the adipose tissue, and the gastrointestinal tract help to set activity and feeding behavior.

P5 Principle 5 (1 of 3)

The metabolic activities of cells and organisms are complex and intertwined; perturbation at one point in the system has far-reaching consequences for health. When the normal energy-yielding metabolism of glucose and fatty acids is impeded by defective insulin signaling, the result is the disease diabetes.

23.1 Hormone Structure and Action

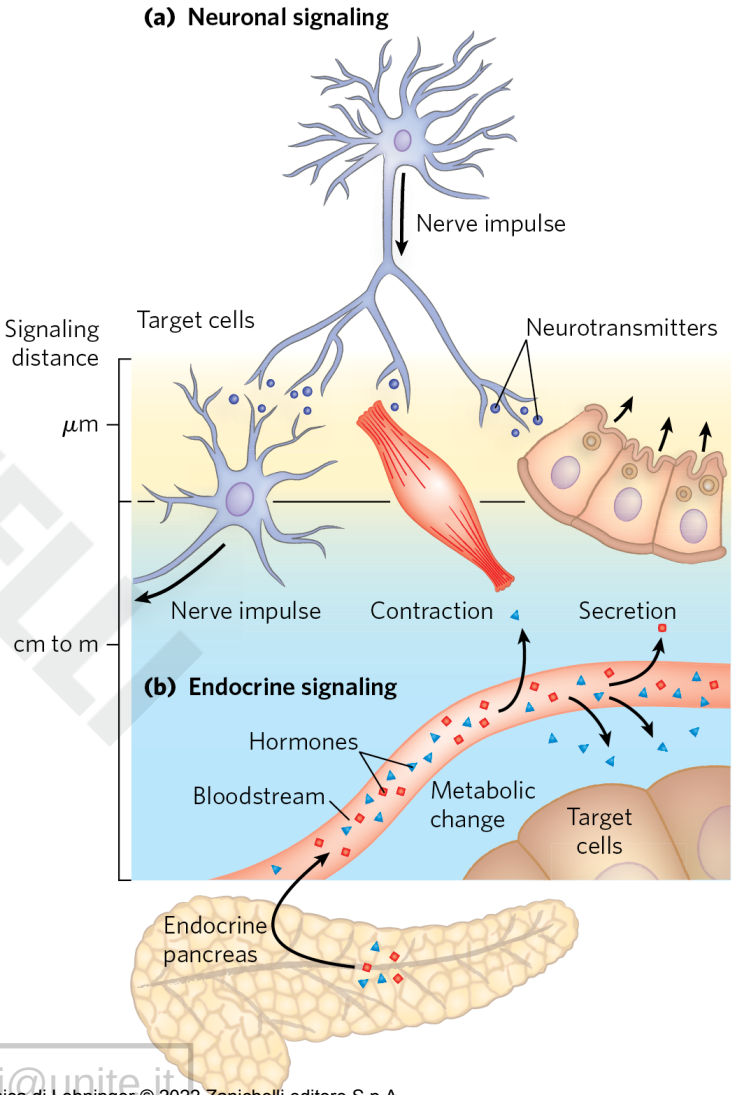
Hormones and the Neuroendocrine System

- **hormones** = small molecules or proteins that are produced in one tissue, released into the bloodstream, and carried to other tissues
  - act through specific receptors to bring about changes in cellular activities
  - serve to coordinate the metabolic activities of several tissues or organs

- **neuroendocrine system** = the system that coordinates metabolism in mammals

Neuronal and Endocrine Signaling

- neuronal signaling = nerve cells release neurotransmitters that act on nearby cells
  - distance may be small (<1 μm)
- endocrine signaling = hormones are carried by the bloodstream to nearby cells or other organs
  - distance may be great (>1 m)

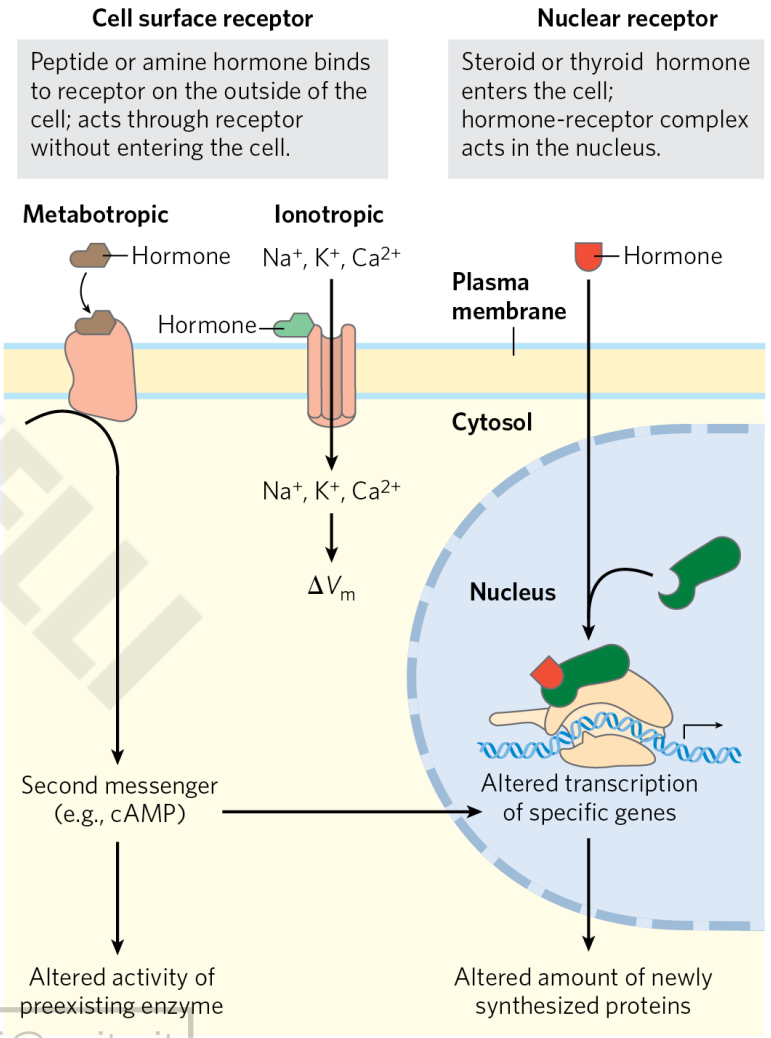


Hormones Act through Specific High-Affinity Cellular Receptors

- four general types of intracellular consequences of ligand-receptor interaction:
  - generation of a second messenger that acts as an allosteric regulator of one or more enzymes
  - activation of a a receptor tyrosine kinase
  - opening or closing of an ion channel causes a change in membrane potential
  - a nuclear hormone receptor protein mediates a change in gene expression

Metabotropic and Ionotropic Surface Receptors

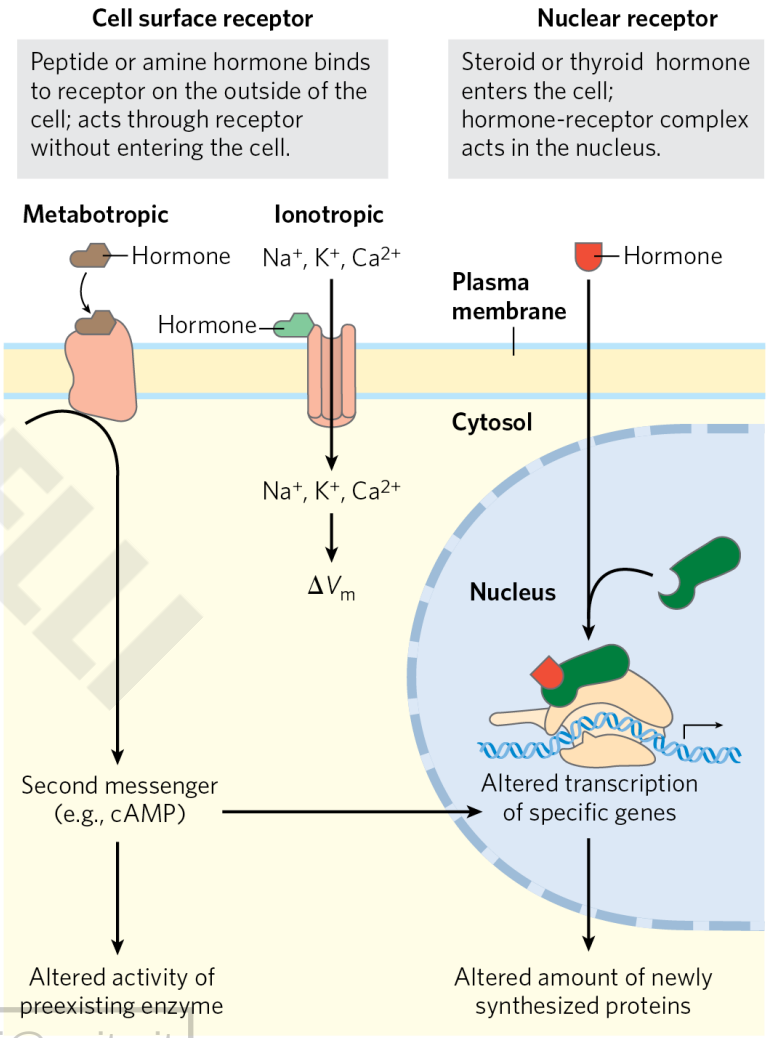
- **metabotropic** = cell surface hormone receptors that activate or inhibit a downstream enzyme
- **ionotropic** = those that open or close an ion channel in the plasma membrane, resulting in a change ΔV_m or ion concentration
- both trigger rapid physiological or biological responses



Water-Insoluble Hormones Pass Through the Plasma Membrane

- water-insoluble hormones = readily enter the cell and bind receptor proteins in the nucleus to alter the expression of specific genes

- promote maximal responses after hours or days



P1 Principle 1 (2 of 4)

The tissues in a mammal are connected by a neurosecretory system that coordinates their activities. Mammals use chemically diverse hormones in a highly specific and multidirectional signaling system, connecting the tissues with each other and with the central nervous system.

Hormones Are Chemically Diverse

TABLE 23-1 Classes of Hormones

Type	Example	Synthetic path	Mode of action
Protein	Insulin (Fig. 23-4)	Proteolytic processing of prohormone	Plasma membrane RTK
Protein	Glucagon		Plasma membrane GPCRs; second messengers
Peptide	Vasopressin (p. 880)		
Catecholamine	Epinephrine (Fig. 22-31)	From tyrosine	
Eicosanoid	Prostaglandin E_2 (Fig. 10-17)	From arachidonate	
Endocannabinoid	Anandamide (Fig. 23-40)		
Steroid	Testosterone (Fig. 10-18)	From cholesterol	Nuclear receptors; transcriptional regulation
Corticosteroid	Cortisol (Fig. 10-18)		
Vitamin D	Calcitriol (Fig. 10-19)		
Retinoid	Retinoic acid (Fig. 10-20)	From vitamin A	
Thyroid	Triiodothyronine (T_3)	From Tyr in thyroglobulin	
Nitric oxide	NO• (Fig. 22-33)	From arginine	Cytosolic receptor; second messenger

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Endocrine, Paracrine, and Autocrine Hormones

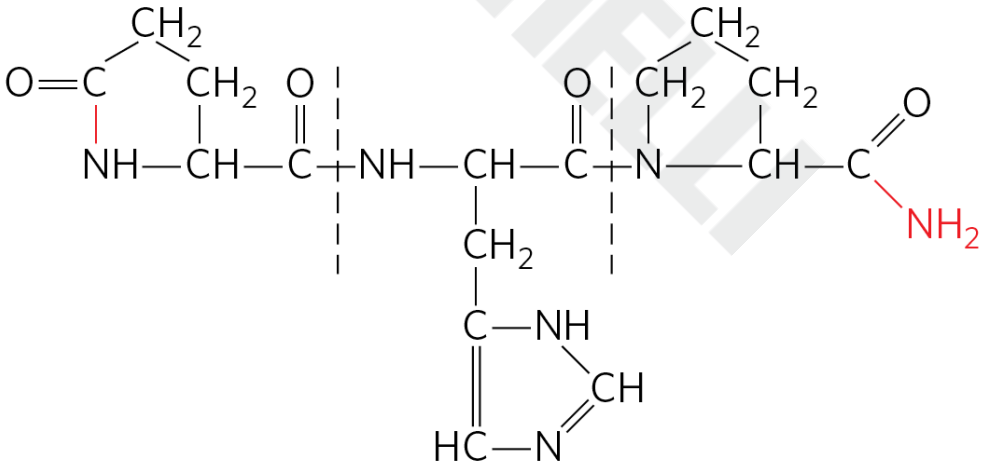
- **endocrine** hormones = released into the blood and carried to target cells throughout the body
  - examples: insulin and glucagon

- **paracrine** hormones = released into the extracellular space and diffuse to neighboring target cells
  - example: eicosanoid hormones

- **autocrine** hormones = affect the same cell that releases them

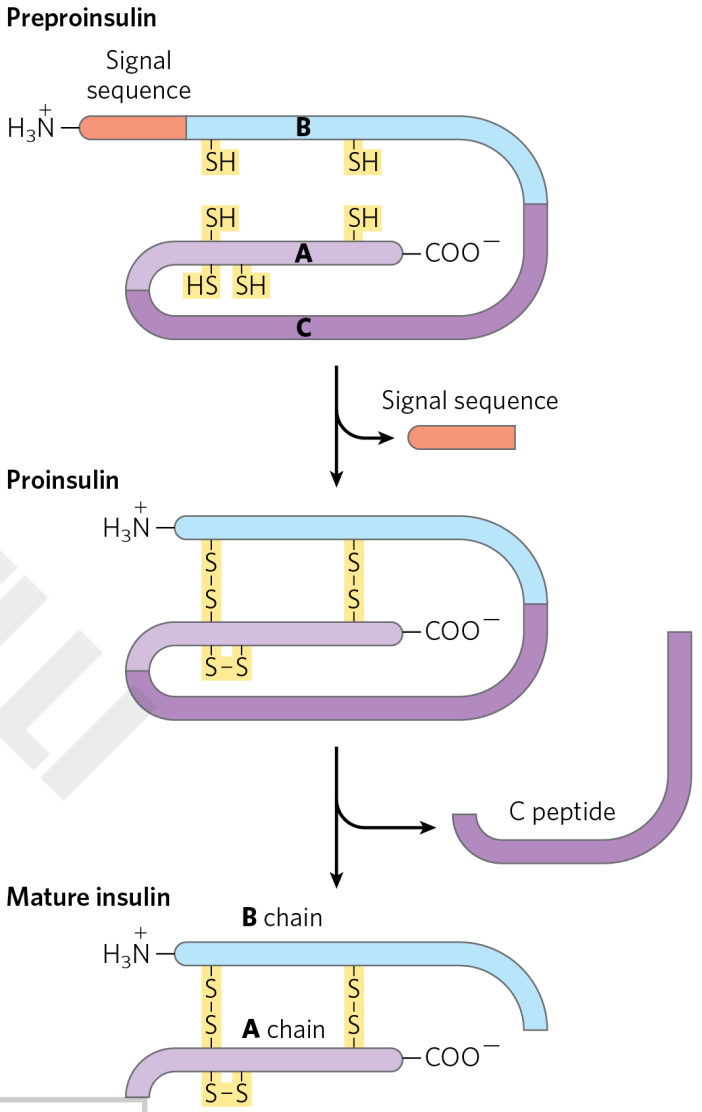
Peptide Hormones

- **peptide hormones** = hormones that are synthesized as proproteins (prohormones) that are activated upon release by proteolytic cleavage
  - vary in size from 3 to >200 amino acid residues
  - examples: insulin, glucagon, somatostatin, calcitonin, and all the hormones of the hypothalamus and pituitary



Insulin is a Peptide Hormone

- **insulin** = a small protein with two polypeptide chains, A and B, joined by two disulfide bonds
  - synthesized on ribosomes in the pancreas as preproinsulin
  - stored as proinsulin in secretory vesicles
  - converted to active insulin by proteases when blood glucose is sufficiently elevated



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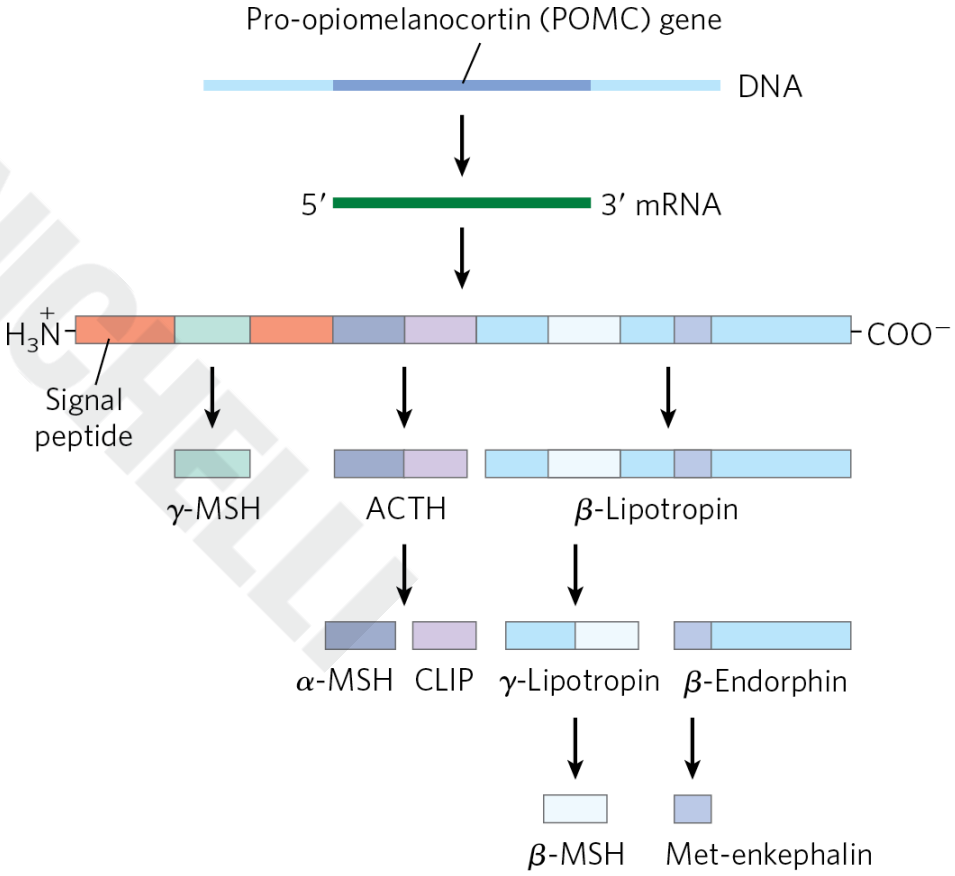
Some Peptide Prohormones Can Yield Multiple Products

- **pro-opiomelanocortin (POMC)** = a proprotein that undergoes specific cleavage to produce several active hormones

- the proprotein is processed differently in different tissues
  - depends on which proteases are expressed



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P1 Principle 1 (3 of 4)

The tissues in a mammal are connected by a neurosecretory system that coordinates their activities. Mammals use chemically diverse hormones in a highly specific and multidirectional signaling system, connecting the tissues with each other and with the central nervous system.

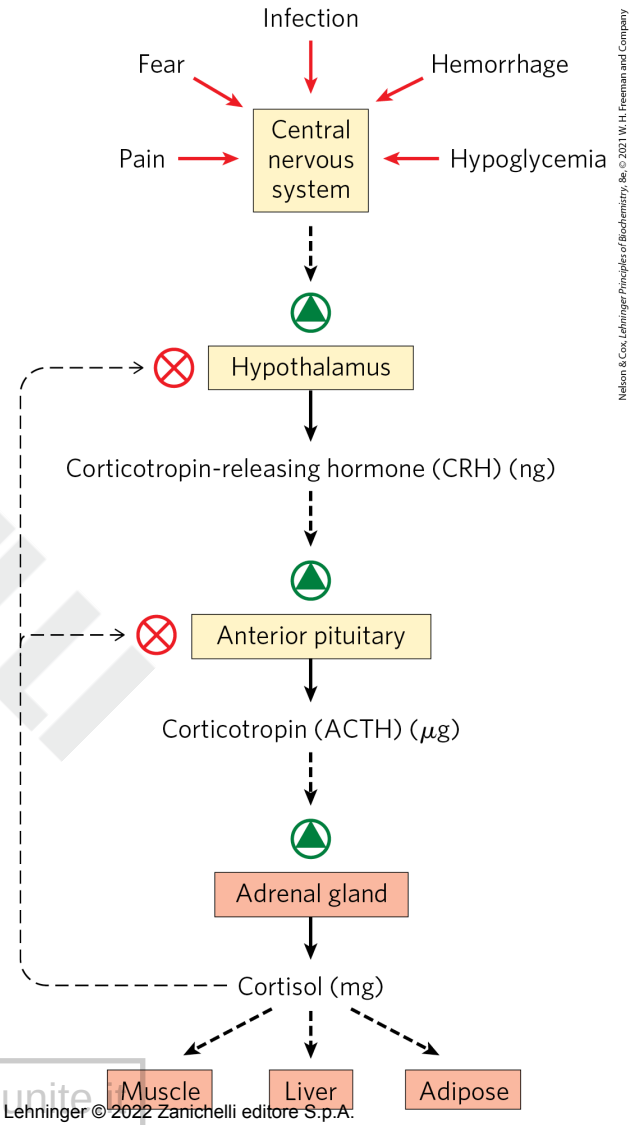
Some Hormones Are Released by a "Top-Down" Hierarchy of Neuronal and Hormonal Signals

- the central nervous system (CNS) receives input from many internal and external sensors and orchestrates the production of appropriate hormonal signals by the endocrine tissues

- **hypothalamus** = the coordination center of the endocrine system
  - receives and integrates messages from the CNS
  - produces releasing factors

Top-Down Hormone Release

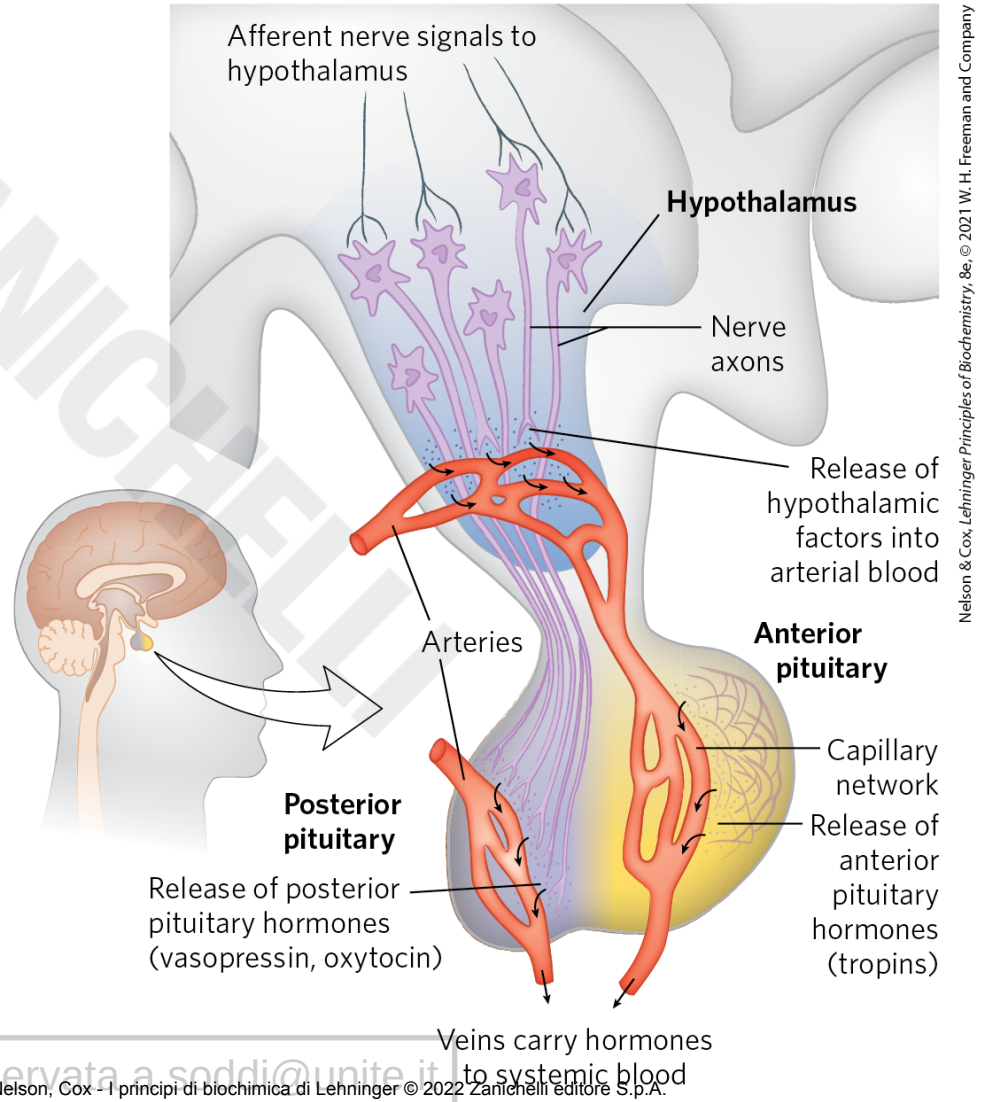
- at each level of a hormonal cascade, feedback inhibition of earlier steps is possible



Neuroendocrine Origins of Hormone Signals

- posterior pituitary = contains the end of axons from the hypothalmus

- anterior pituitary = the endocrine organ that receives releasing factors from the hypothalamus via blood vessels



Hormonal Cascades Result in Large Signal Amplifications

- at each level in the cascade, a small signal elicits a larger response

- the cortisol hormone cascade has an overall amplification of at least a millionfold:

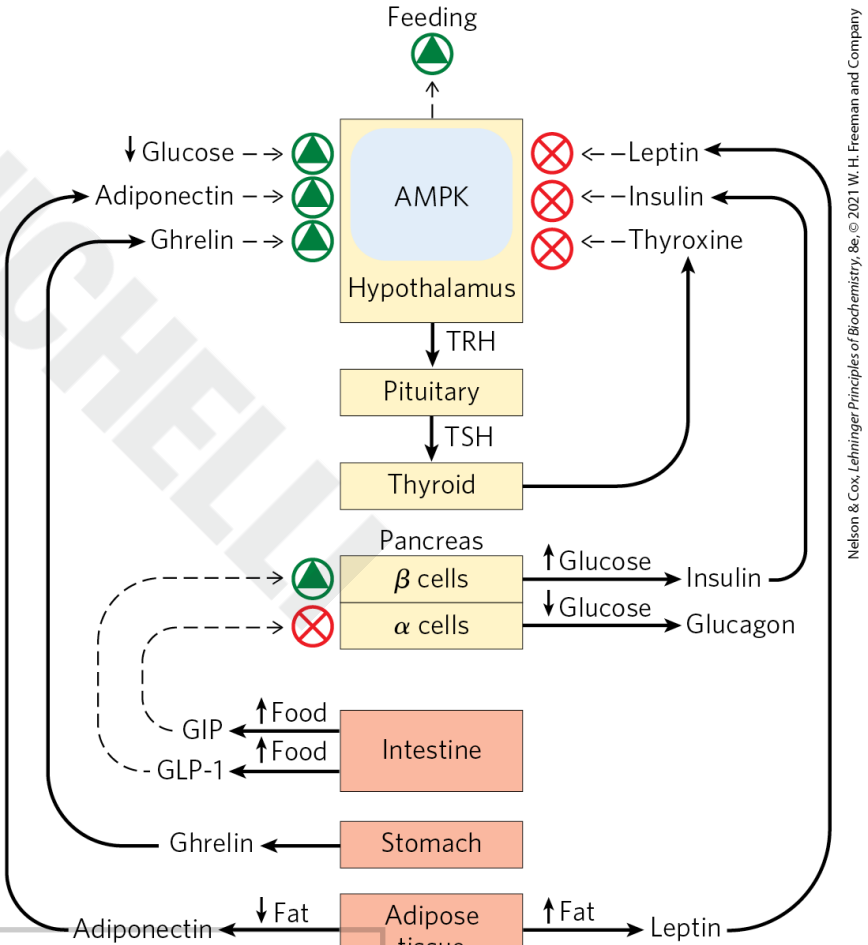
  initial signal to the hypothalamus⟶ release of CRH (ng) ⟶
  release of corticotropin (*μ*g) ⟶ release of cortisol (mg)

P1 Principle 1 (4 of 4)

The tissues in a mammal are connected by a neurosecretory system that coordinates their activities. Mammals use chemically diverse hormones in a highly specific and multidirectional signaling system, connecting the tissues with each other and with the central nervous system.

"Bottom-Up" Hormonal Systems Send Signals Back to the Brain and to Other Tissues

- some hormones are produced in the digestive tract, muscle, and adipose tissue and communicate the current metabolic state to the hypothalamus



Adipokines

- **adipokines** = peptide hormones produced in adipose tissue that signal the adequacy of fat reserves

- **leptin** = an adipokine released when adipose tissue is well-filled with triacylglycerols
  - acts in the brain to inhibit feeding

- **adiponectin** = an adipokine released when adipose tissue is depleted of fat reserves
  - acts in the brain to stimulate feeding

Ghrelin and Incretins

- **ghrelin** = produced in the gastrointestinal tract when the stomach is empty
  - acts in the hypothalamus to stimulate feeding

- **incretins** = peptide hormones produced in the gut after ingestion of a meal
  - acts in the pancreas to increase insulin secretion and decreases glucagon secretion

Neuropeptide Y, Peptide YY, and Irisin

- **neuropeptide Y (NPY)** = a hormone produced in the hypothalamus and in the adrenal glands
  - promotes feeding and reduces nonessential energy expenditure

- **peptide YY (PYY3–36)** = a hormone produced in the intestine
  - signals satiety in the brain

- **irisin** = a peptide hormone produced in muscle from exercise
  - acts to convert white adipose tissue into beige adipose tissue

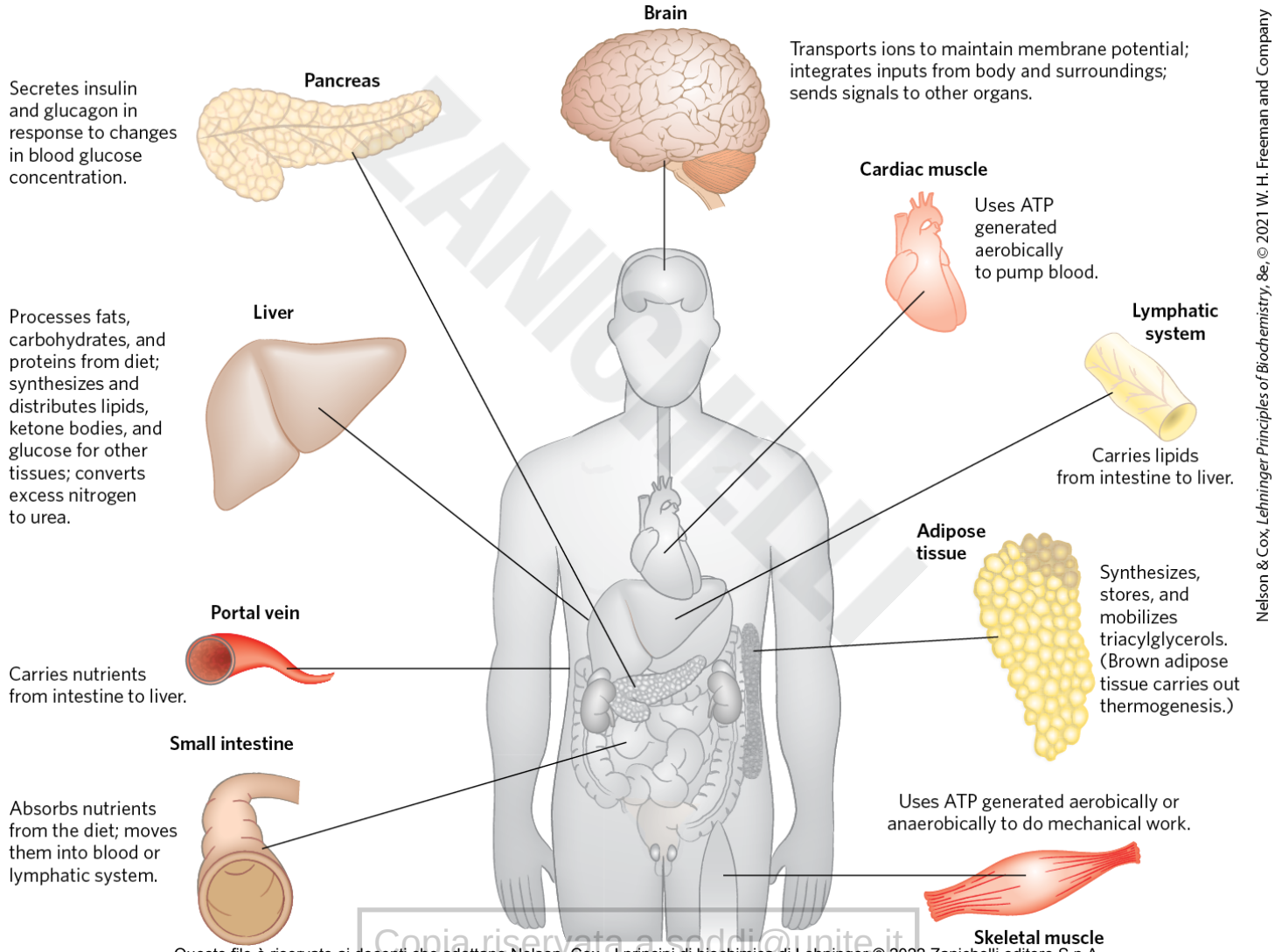
Peptide Hormones That Act on Feeding Behavior and Fuel Selection in Mammals

Table 23-2 Some Peptide Hormones That Act on Feeding Behavior and Fuel Selection in Mammals

Hormone	Production site(s)	Target tissue(s)	Action(s)
Insulin	Pancreatic β cells	Muscle, adipose, liver	Stimulates glucose uptake and synthesis of glycogen and fat
Glucagon	Pancreatic α cells	Liver, adipose	Stimulates gluconeogenesis and glucose release to blood
Leptin	Adipose tissue	Hypothalamus	Reduces hunger
Adiponectin	Adipose tissue	Muscle, liver, others	Stimulates catabolism and feeding behavior
Ghrelin	Stomach, intestine	Brain	Signals hunger
Incretins: GLP-1, GIP	Intestine	Pancreas	Stimulate insulin release
NPY	Hypothalamus, adrenals	Brain, autonomic nervous system	Stimulates feeding behavior
$PYY_{3–36}$	Intestine	Brain	Signals satiety
Irisin	Muscle (after exercise)	Adipose	Turns white adipose tissue to beige

23.2 Tissue-Specific Metabolism

Specialized Metabolic Functions of Mammalian Tissues



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The Liver Processes and Distributes Nutrients

- the liver is the central processing and distribution organ for nutrients
  - can adjust metabolism to meet changing circumstances

- sugars, amino acids, and some reconstituted TAGs pass from intestinal epithelial cells to the liver via the portal vein

The Liver Has Two Main Cell Types

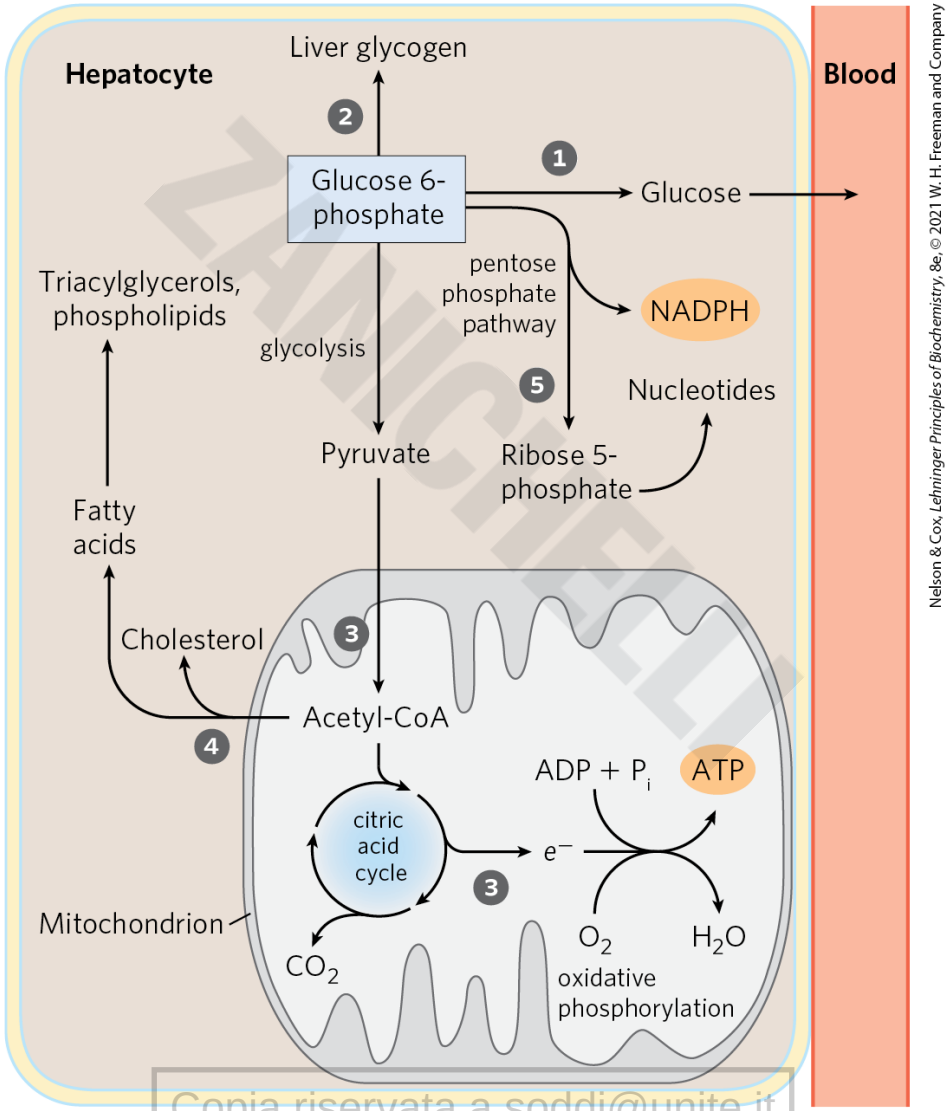
- Kupffer cells = phagocytes that are important in immune function

- **hepatocytes** = transform dietary nutrients into the fuels and precursors required by other tissues and export them via the blood

Carbohydrates

- glucose 6-phosphate may:
  - be exported as glucose to replenish blood glucose
  - be used to synthesize glycogen or fatty acids
  - enter the citric acid cycle (following glycolysis and the pyruvate dehydrogenase reaction) to produce ATP
  - enter the pentose phosphate pathway to yield NADPH and pentoses

Metabolic Pathways for Glucose 6-Phosphate in the Liver



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Xenobiotics

- **xenobiotics** = compounds that do not occur naturally but are the products of human activity
  - examples: drugs, food additives, and preservatives

- xenobiotics are metabolized in the liver
  - NADPH is an essential cofactor

Amino Acids

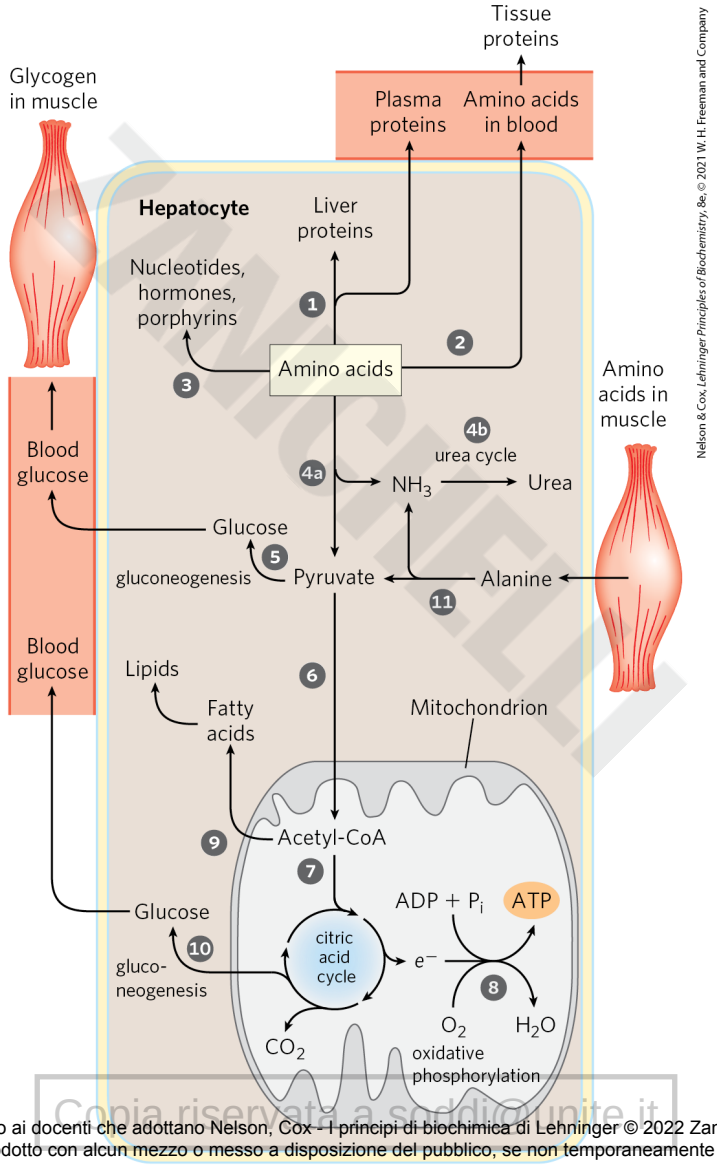
- amino acids may:
  - be used to synthesize liver and plasma proteins
  - enter the bloodstream to pass to other organs
  - be used as biosynthetic precursors for proteins, nucleotides, hormones, etc. in the liver
  - be converted to pyruvate and ammonia
    - ammonia is converted to urea

Possible Fates of Pyruvate and Acetyl CoA from Amino Acids

- pyruvate formed from amino acids may be converted to:
  - glucose and glycogen via gluconeogenesis
  - acetyl-CoA

- fates of acetyl-CoA include:
  - oxidation via the citric acid cycle and oxidative phosphorylation to produce ATP
  - conversion to lipids for storage

Metabolic Pathways for Amino Acids in the Liver



P2 Principle 2 (2 of 3)

Among the tissues and organs of an animal, there is a striking division of labor. The specialized role of each organ is reflected in its metabolic activities and capabilities. The circulatory system connects all of the tissues by carrying hormonal signals and metabolites between and among them.

Metabolism of Amino Acids from Muscle

- during prolonged intervals between meals, some muscle protein is degraded to amino acids
- the amino acids undergo transamination to pyruvate to yield alanine
- in hepatocytes:
  - alanine in deaminated to yield pyruvate, which enters gluconeogenesis
  - ammonia is converted to urea for excretion

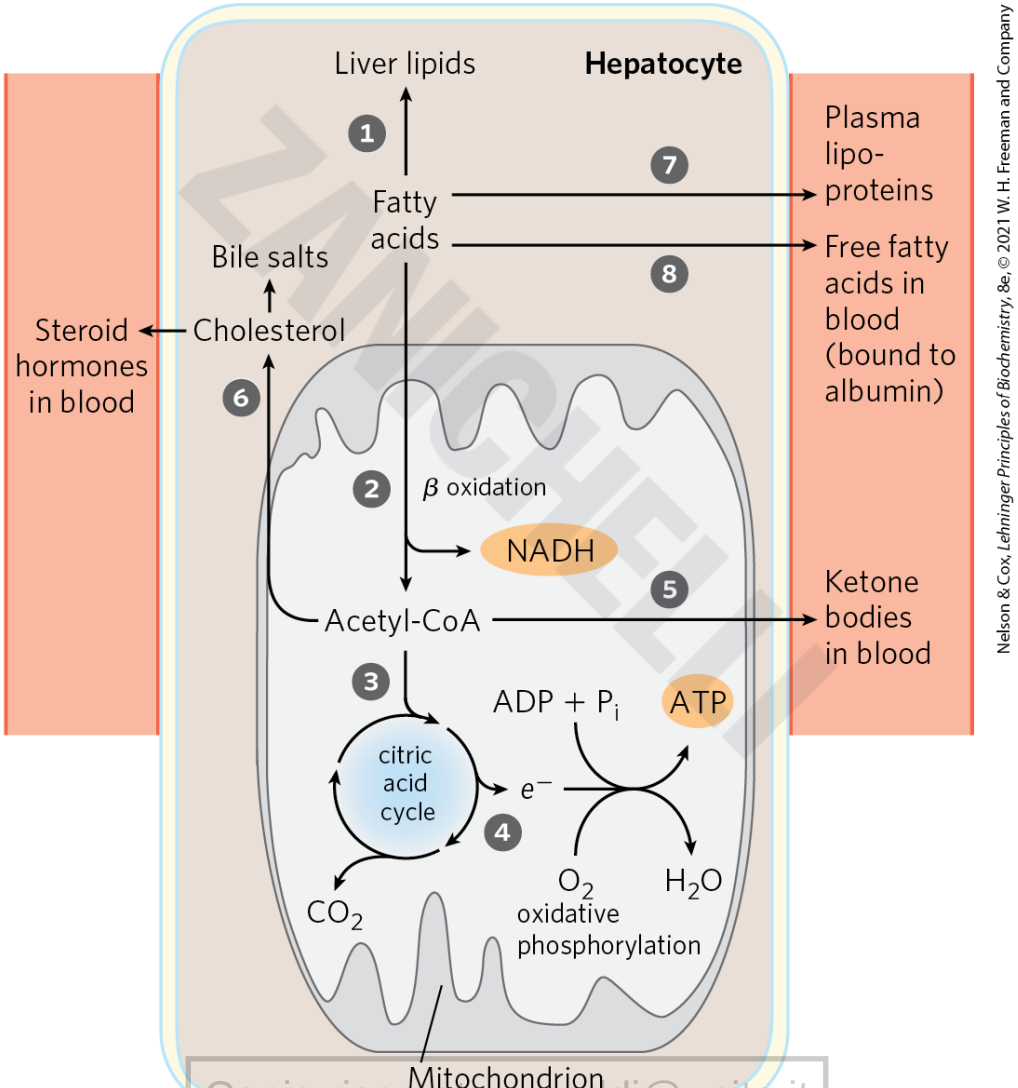
Lipids

- lipids may:
  - be converted to liver lipids
  - undergo β oxidation to form acetyl-CoA and NADH
  - be converted to the phospholipids and TAGs of plasma lipoproteins
  - bind to albumin in the blood for transport to the heart and skeletal muscles

Possible Fates of Acetyl CoA from Lipids

- fates of acetyl-CoA from lipids include:
  - oxidation via the citric acid cycle and oxidative phosphorylation to produce ATP
  - conversion to acetoacetate and *β*-hydroxybutyrate (ketone bodies)
  - biosynthesis of cholesterol, steroid hormones, and bile salts

Metabolic Pathways for Lipids in the Liver



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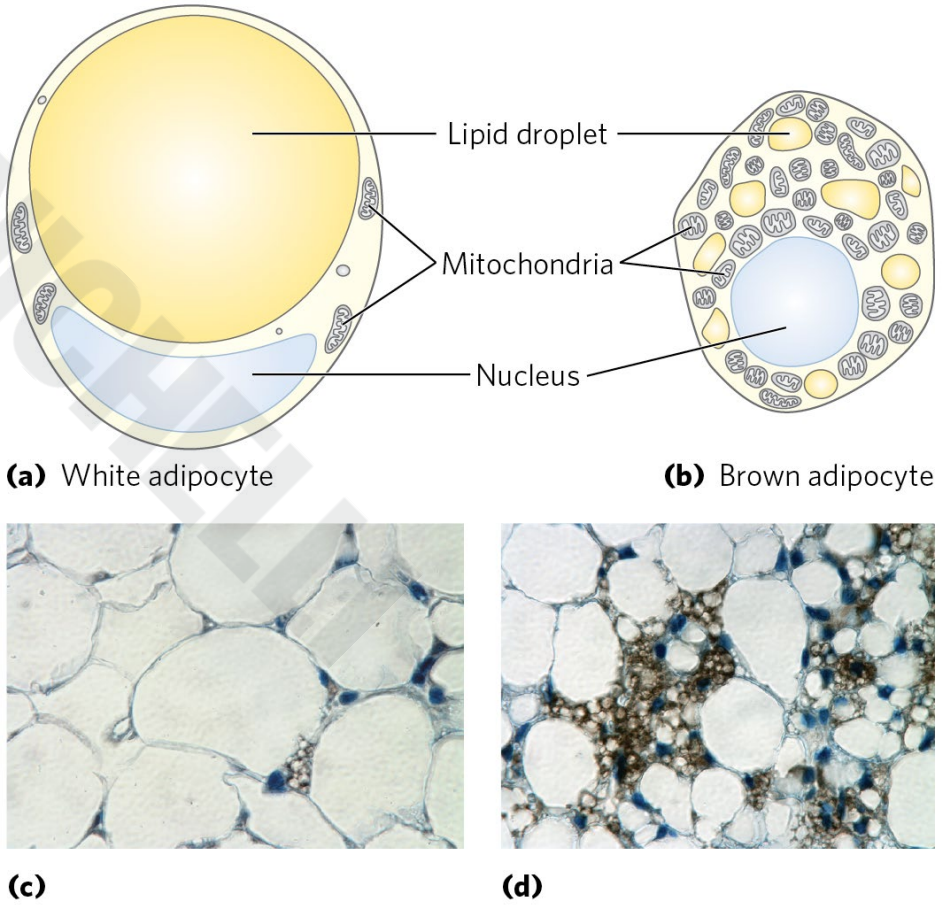
Adipose Tissues Store and Supply Fatty Acids

- **white adipose tissue (WAT)** = adipose tissue located under the skin, around deep blood vessels, and in the abdominal cavity
  - its **adipocytes** are large, spherical cells filled with a single lipid droplet containing TAGs and sterol esters



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WAT Releases TAGs in Response to Epinephrine

- lipases hydrolyze stored TAGs to release FFAs
  - activity is stimulated by epinephrine and phosphorylation
  - activity is decreased by insulin

Brown and Beige Adipose Tissues Are Thermogenic

- **brown adipose tissue (BAT)** = adipose tissue specialized for thermogenesis
  - its adipocytes are smaller, polygonal cells filled with multiple smaller lipid droplets
  - contain more mitochondria
  - contain a richer supply of capillaries and innervation

(a) Adam Steinberg. (b) Reprinted with permission of American Diabetes Association, from M. Saito et al., *Diabetes* 58:1526, 2009. Fig. 1; permission conveyed through Copyright Clearance Center, Inc.

Uncoupling Protein 1 is Responsible for Thermogenesis

- **uncoupling protein 1 (UCP1)** = protein produced by BAT that allows the H^+ gradient in mitochondria to be dissipated as heat in a process is known as **thermogenesis**
  - keeps organs warm in low temperature environments

Beige Adipocytes

- **beige adipocytes** = adipocytes that can be converted by cold exposure or by β-adrenergic stimulation into cells very similar to brown adipocytes
  - have multiple lipid droplets
  - are richer in mitochondria than white adipocytes
  - produce UCP1

Muscles Use ATP for Mechanical Work

- **myocytes** = skeletal muscle cells

- metabolism in myocytes is specialized to generate and use ATP for contraction

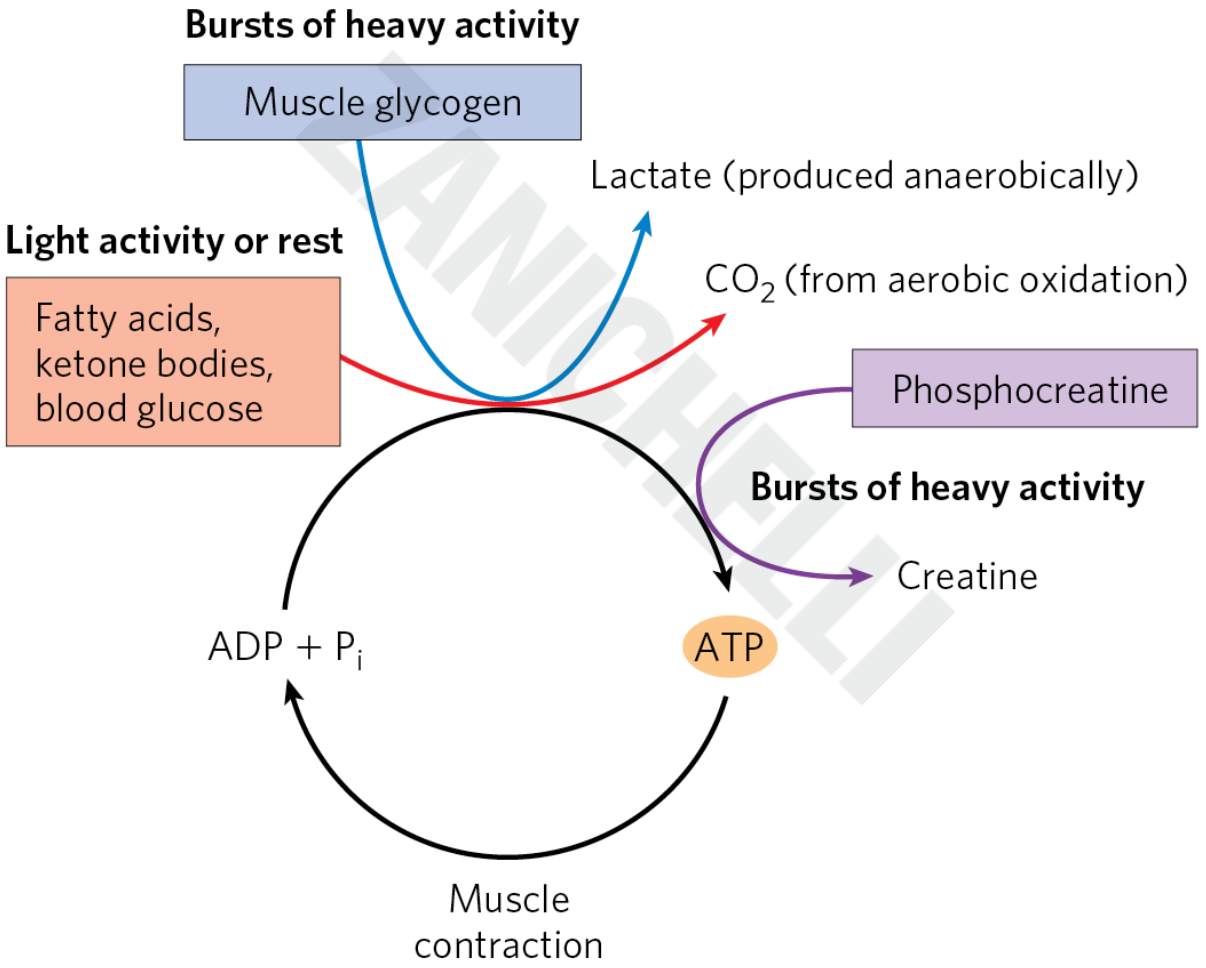
Slow-Twitch Muscle

- **slow-twitch muscle** (red muscle) = provides relatively low tension but is highly resistant to fatigue
  - produces ATP by oxidative phosphorylation
  - very rich in mitochondria
  - served by dense networks of blood vessels which bring oxygen

Fast-Twitch Muscle

- **fast-twitch muscle** (white muscle) = can develop greater tension and do so faster, but is quicker to fatigue
  - has fewer mitochondria than red muscle
  - is less well-supplied with blood vessels
  - uses ATP faster than it can replace it

Energy Sources for Muscle Contraction



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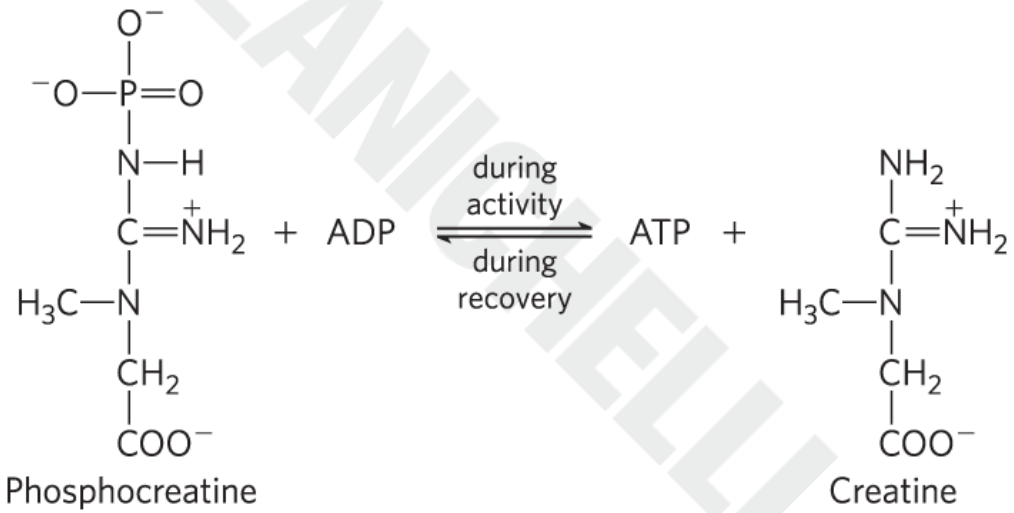
The Creatine Kinase Reaction

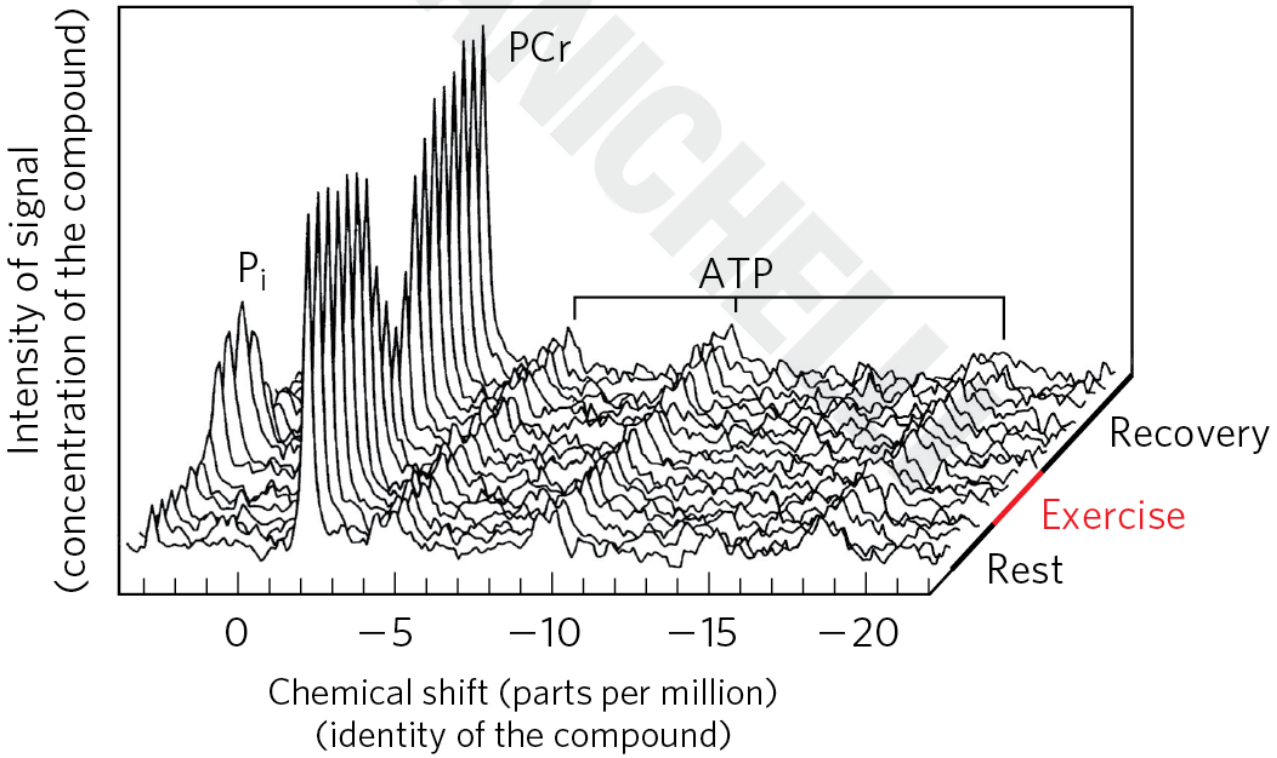
- creatine kinase = uses phosphocreatine to rapidly regenerate ATP from ADP



- creatine shuttles ATP equivalents from the mitochondrion to sites of ATP consumption

Phosphocreatine Buffers ATP Concentration During Exercise

- the ATP signal barely changes during exercise due to continued respiration and the reservoir of phosphocreatine



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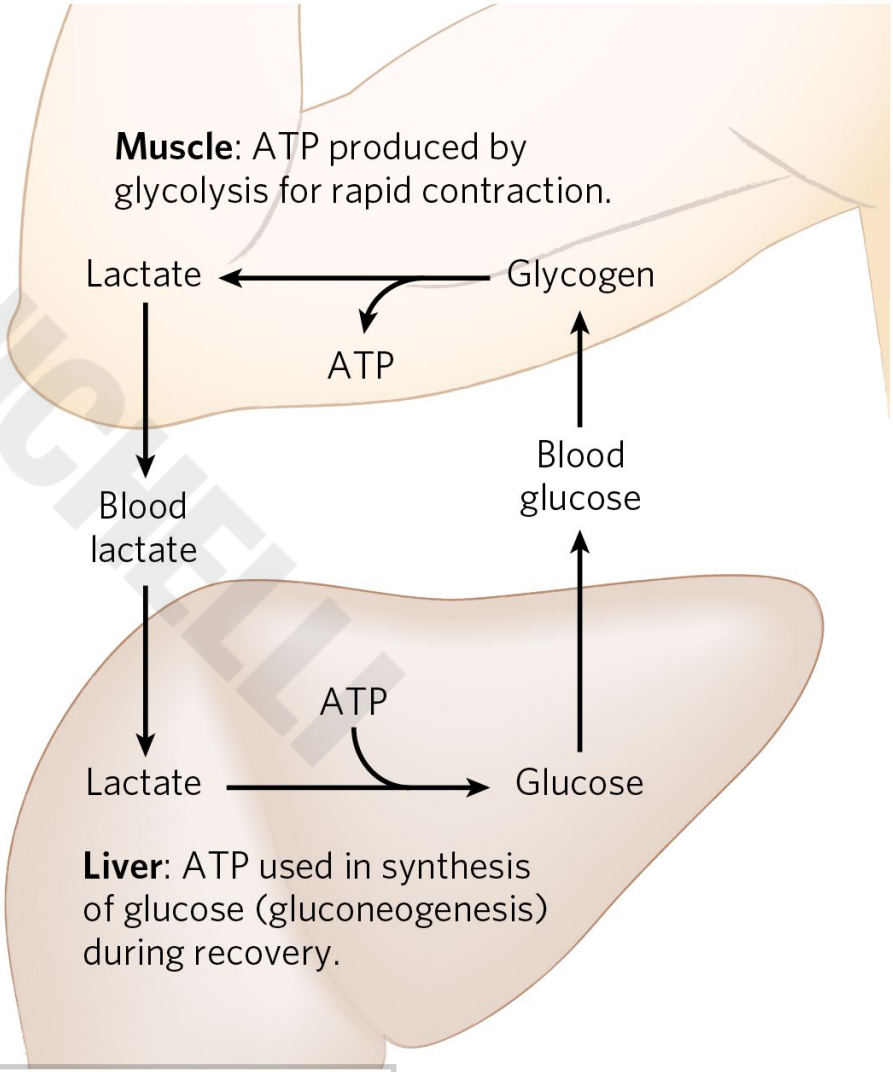
The Cori Cycle

- during recovery, lactate is transported to the liver and converted to glucose by gluconeogenesis
- glucose is released to the blood and returned to the muscles to replenish their glycogen stores



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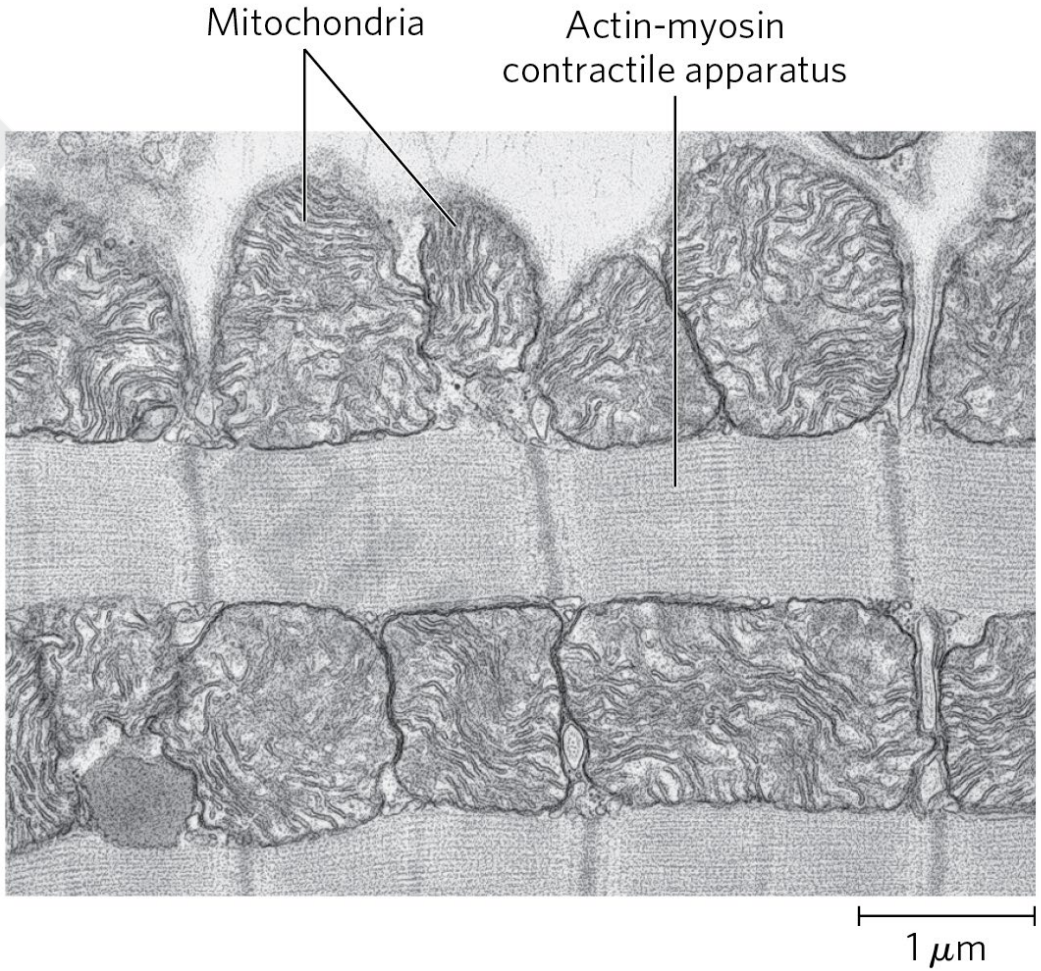
Shivering Thermogenesis

- **shivering thermogenesis** = rapidly repeated muscle contraction that produces heat but little motion
  - helps maintain the body at its preferred temperature of 37°C

The Heart Mainly Uses FFAs as an Energy Source

- heart muscle obtains nearly all its ATP from oxidative phosphorylation

- fatty acids are the primary fuel
  - glucose and ketone bodies are also oxidized aerobically



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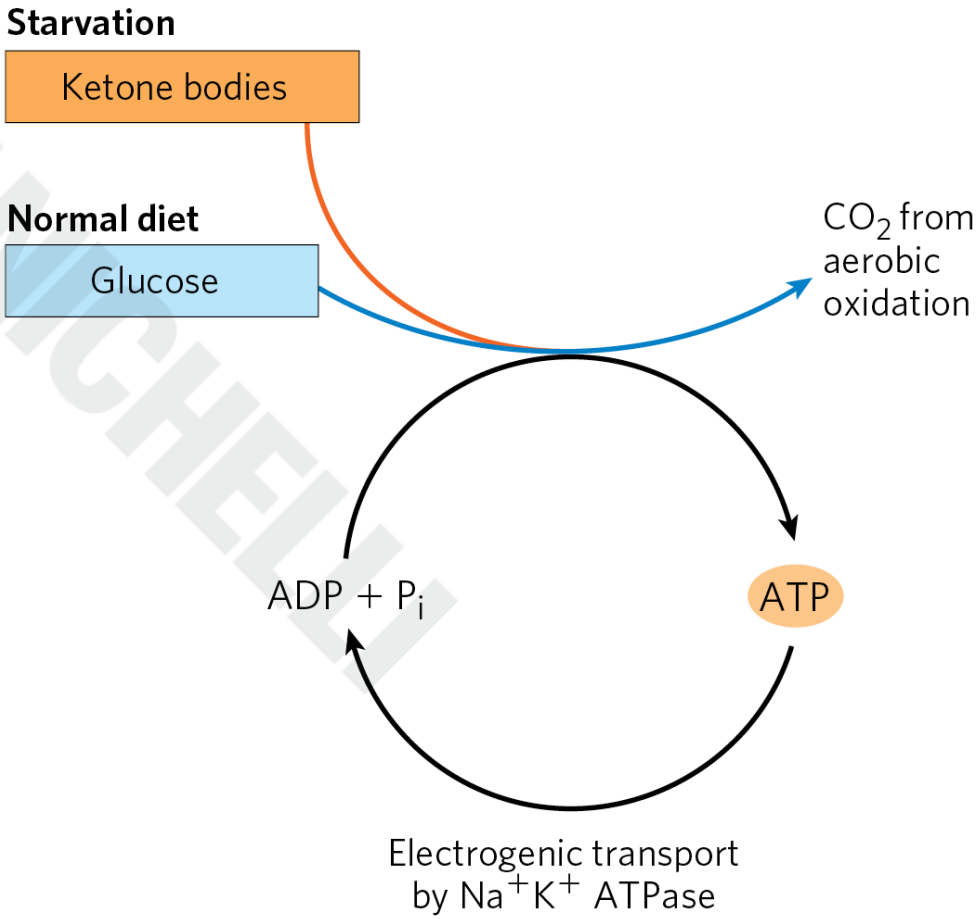
The Brain Uses Energy for Transmission of Electrical Impulses

- neurons of the brain normally use only glucose
- most ATP comes from oxidative phosphorylation



P3 Principle 3 (2 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

Neurons Can Oxidize β-Hydroxybutyrate

- neurons of the brain cannot directly use free fatty acids or lipids from the blood as fuels

- neurons can oxidize β-hydroxybutyrate (a ketone body)
  - important during prolonged fasting or starvation
  - allows the brain to use body fat as an energy source and spare muscle proteins

The Brain Uses ATP to Create and Maintain the Electrical Potential

- the membrane contains an electrogenic ATP-driven antiporter, the Na^+K^+ ATPase

- **action potential** = an electrical signal resulting from transmembrane potential changes
  - serve as the main mechanism of information transfer in the nervous system
  - requires ATP

P2 Principle 2 (3 of 3)

Among the tissues and organs of an animal, there is a striking division of labor. The specialized role of each organ is reflected in its metabolic activities and capabilities. The circulatory system connects all of the tissues by carrying hormonal signals and metabolites between and among them.

Blood Carries Oxygen, Metabolites, and Hormones

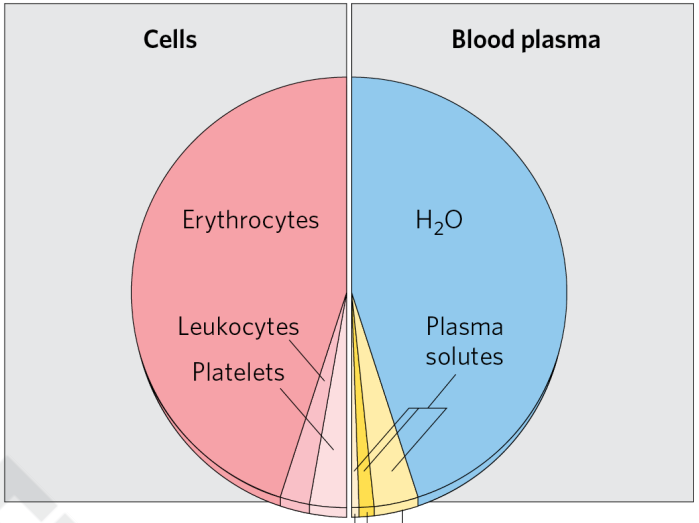
- blood mediates the metabolic interactions among all tissues
  - transports nutrients
  - transports waste products
  - moves O_2 and CO_2 generated
  - carries hormonal signals

The Three Types of Blood Cells

- **erythrocytes** (red cells) = filled with hemoglobin and specialized for carrying O_2 and CO_2
- **leukocytes** (white cells) = central to the immune system to defend against infections
  - include **lymphocytes**
- **platelets** (cell fragments) = help to mediate blood clotting.

The Composition of Blood (By Weight)

- **blood plasma** = the liquid portion of blood
  - 90% water and 10% solutes
- **plasma proteins** = immunoglobulins, serum albumin, apolipoproteins, transferrin, and blood-clotting proteins
  - make up more than 70% of the plasma solids



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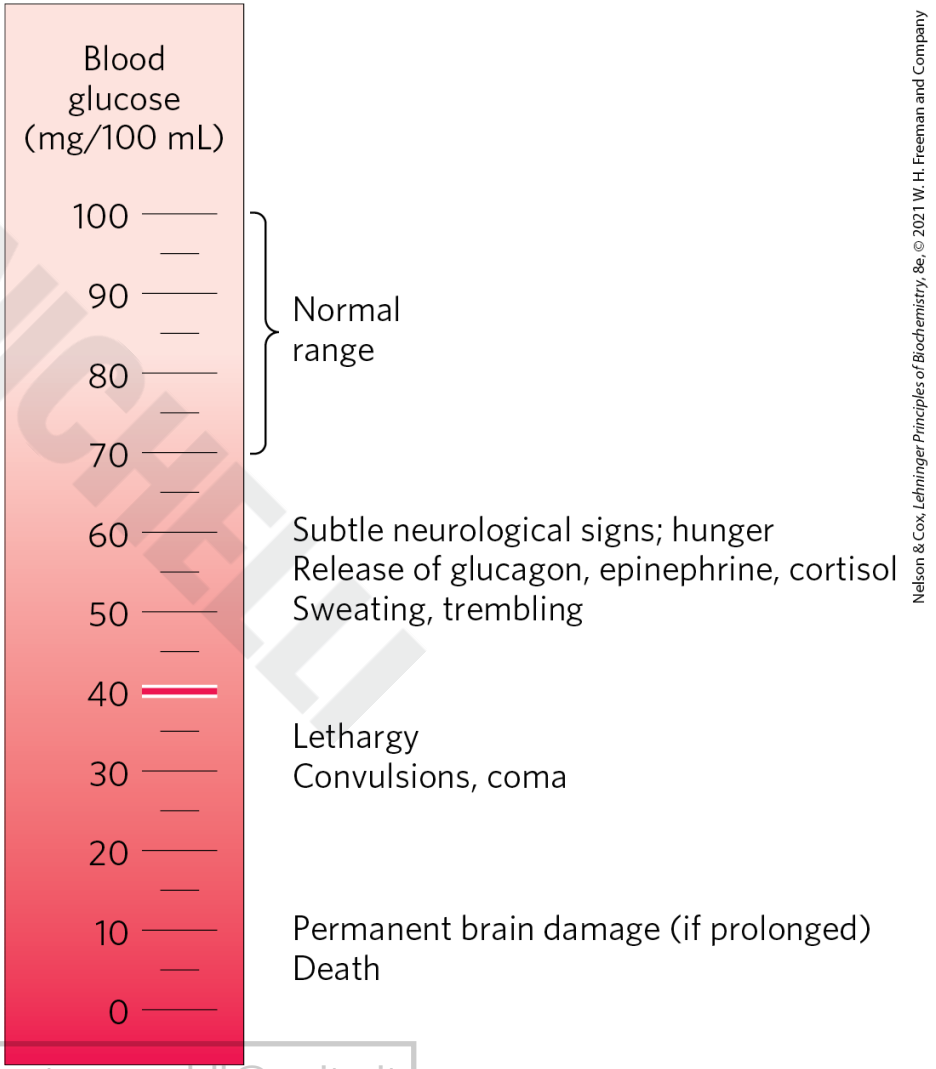
Inorganic components (10%)
NaCl, bicarbonate, phosphate, $CaCl_2$, $MgCl_2$, KCl, Na_2SO_4

Organic metabolites and waste products (20%)
glucose, amino acids, lactate, pyruvate, ketone bodies, citrate, urea, uric acid

Plasma proteins (70%)
Major plasma proteins: serum albumin, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), immunoglobulins (hundreds of kinds), fibrinogen, prothrombin, many specialized transport proteins such as transferrin

Physiological Effects of Low Blood Glucose

- blood glucose is ideally kept at ~4.5 mM (60–90 mg/dL)
- some fluctuations occur after a meal



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23.3 Hormonal Regulation of Fuel Metabolism

P3 Principle 3 (3 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

Maintaining Blood Glucose Levels Requires the Combined Actions of Multiple Hormones

- minute-by-minute adjustments that keep the blood glucose level near 4.5 mM involve the combined actions of:
  - insulin
  - glucagon
  - epinephrine
  - cortisol

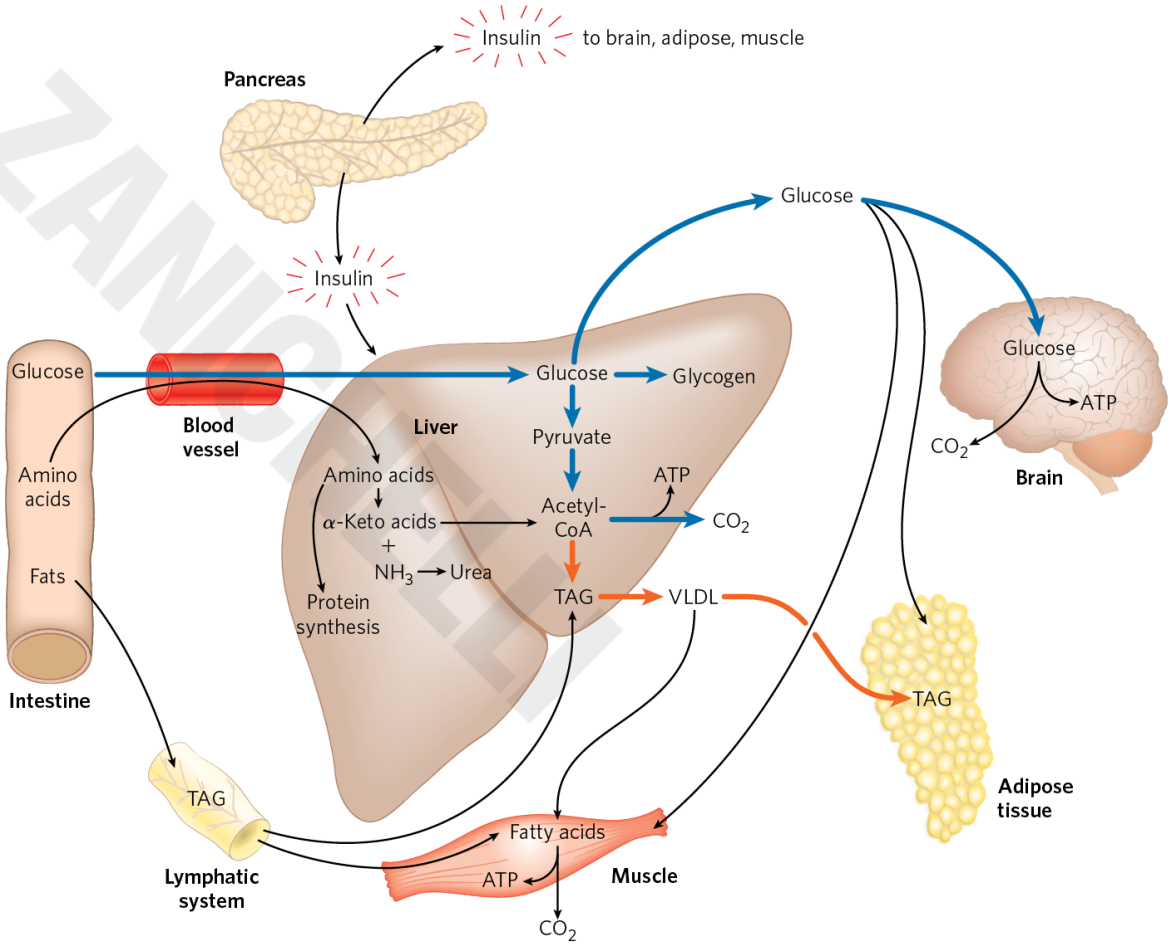
Insulin Counters High Blood Glucose in the Well-Fed State

Table 23-3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose tissue)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by PFK-2) ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

The Well-Fed State: The Lipogenic Liver

- insulin brings about the conversion of excess blood glucose after a meal to:
  - glycogen in the liver and muscle
  - TAGs in adipose tissue



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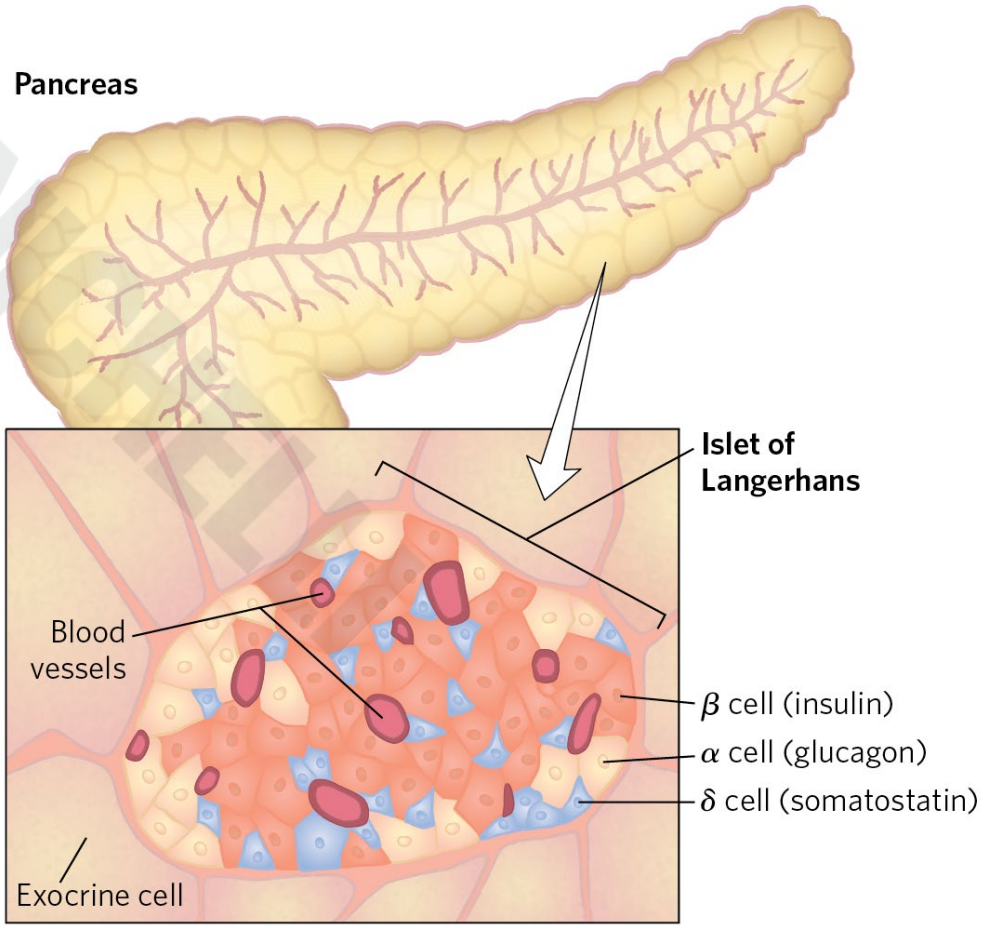
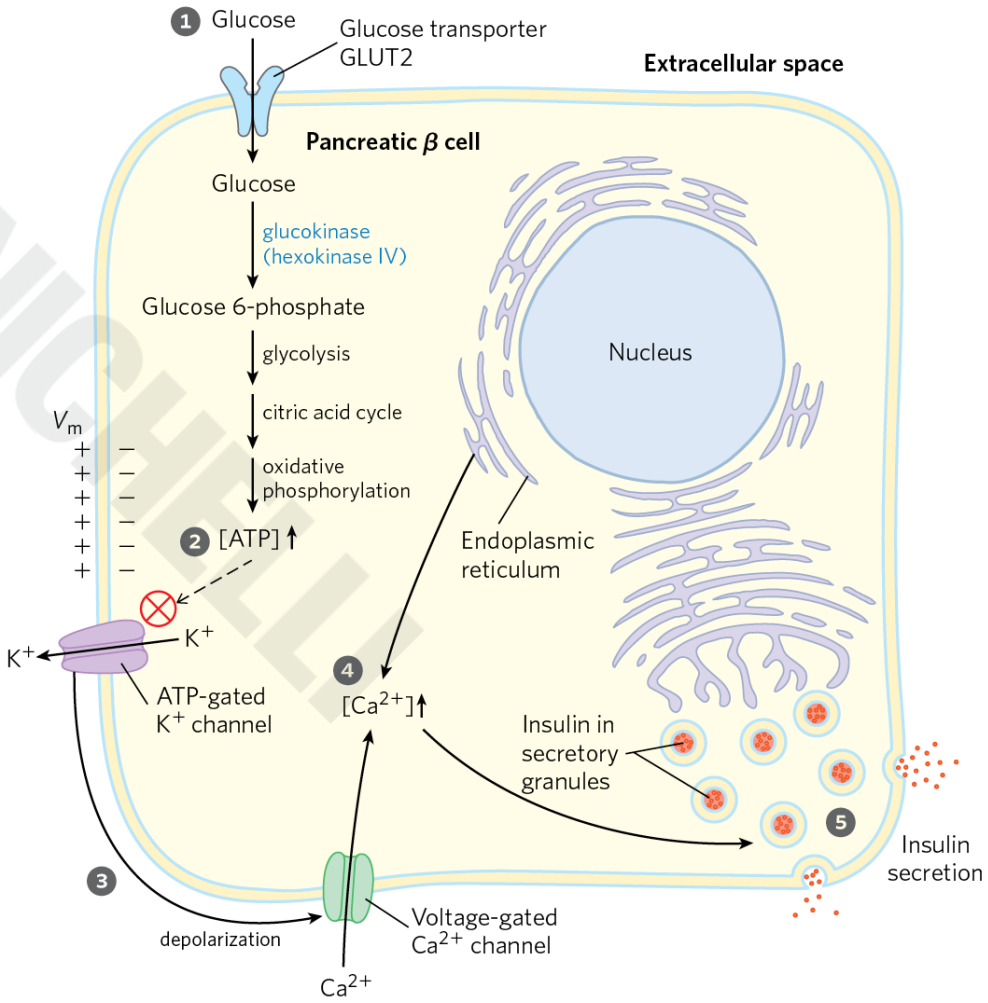
Pancreatic β Cells Secrete Insulin in Response to Changes in Blood Glucose

- islets of Langerhans = clusters of specialized pancreatic cells
  - each cell type produces a single hormone
- increase in blood glucose causes the pancreas to secrete insulin and decrease secretion of glucagon



Glucose Regulation of Insulin Secretion by Pancreatic β Cells

- increased [ATP] closes **ATP-gated K^+ channels**
  - depolarizes the membrane, leading to the opening of voltage-gated Ca^{2+} channels
- the increase in cytosolic [Ca^{2+}] triggers the release of insulin by exocytosis



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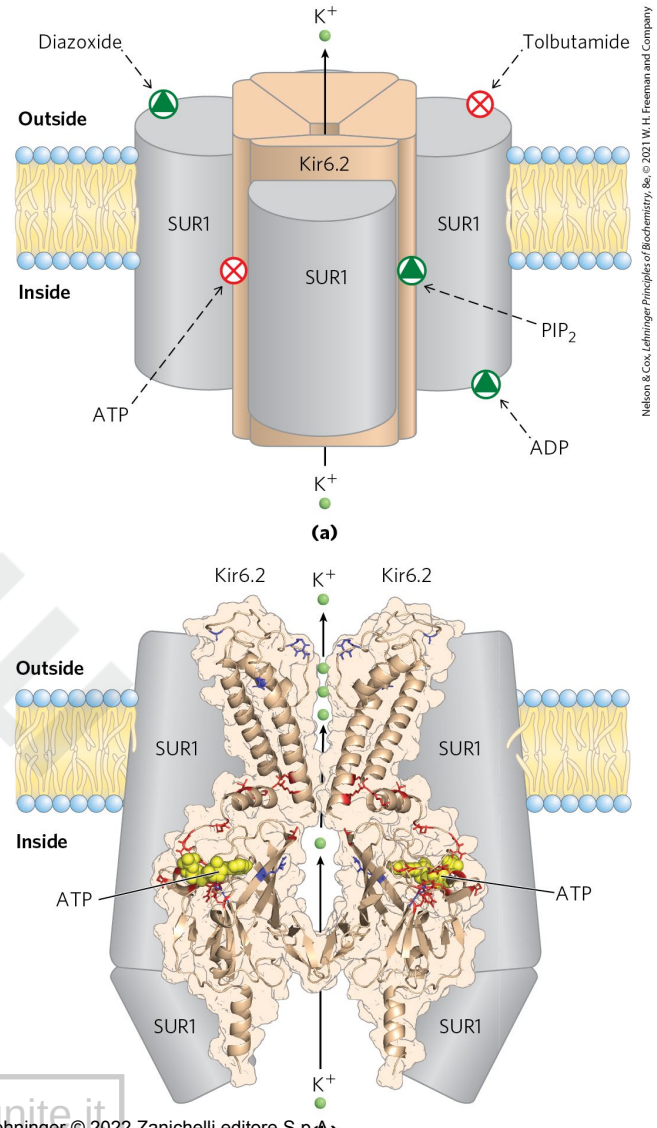
A Simple Feedback Loop Limits Insulin Release

- insulin lowers blood glucose by stimulating glucose uptake
- reduced blood glucose is detected by the β cell as a diminished flux through the glucokinase reaction
  - this slows or stops the release of insulin

ATP-Gated K^+ Channels in β Cells

- channels are octamers:
  - four identical Kir6.2 subunits
  - four identical SUR1 subunits

- **sulfonylurea drugs** = oral medications used in the treatment of type 2 diabetes mellitus
  - bind to the SUR1 subunits, closing the channels and stimulating insulin release



P3 Principle 3 (4 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

Glucagon Counters Low Blood Glucose

- glucagon enables the liver to restore blood glucose to its normal level by:
  - stimulating glycogen breakdown
  - preventing glycolysis
  - promoting gluconeogenesis

TABLE 23-4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

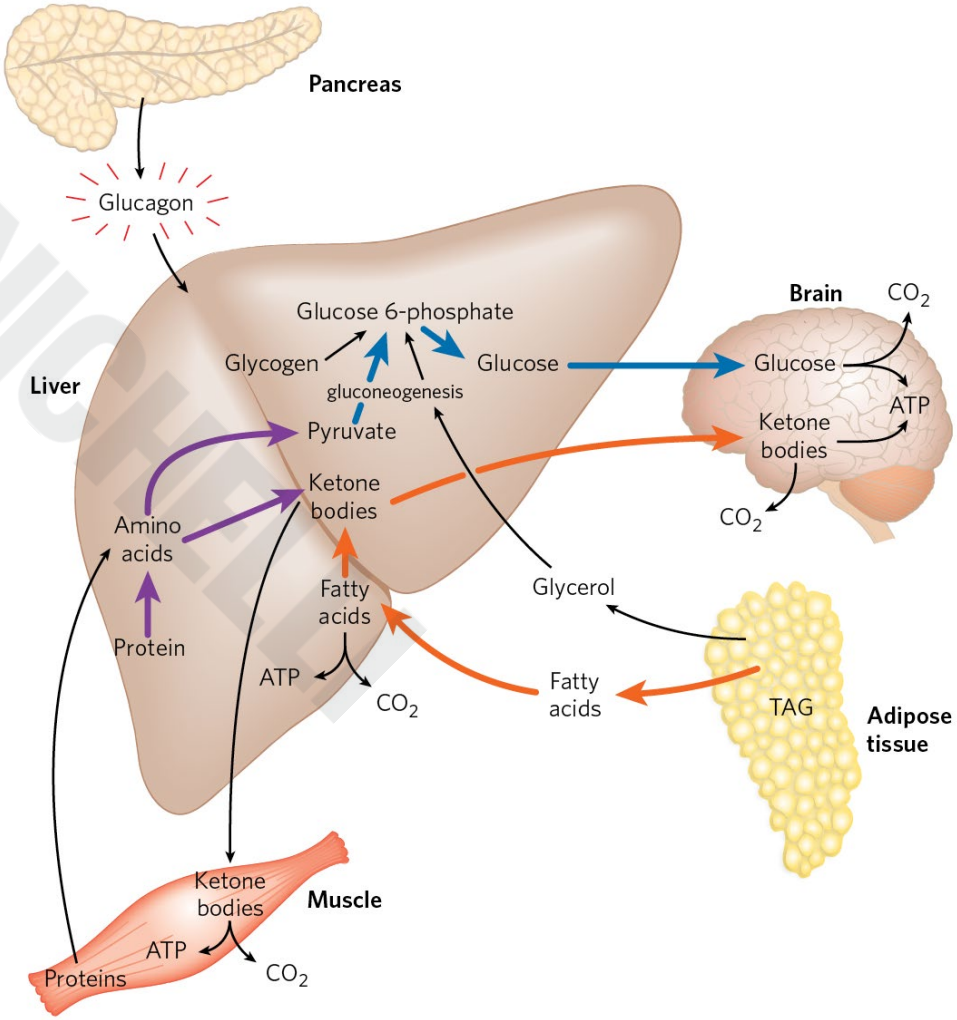
Metabolic effect	Effect on glucose metabolism	Target enzyme
↑ Glycogen breakdown (liver)	Glycogen ⟶ glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate ⟶ glucose	↑ FBPase-2 ↓ Pyruvate kinase ↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Hormone-sensitive lipase
		↑ PKA (perilipin–Ⓟ)
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↓ Acetyl-CoA carboxylase

P3 Principle 3 (5 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

The Fasted State: The Glucogenic Liver

- lowered blood glucose triggers the pancreas to secrete **glucagon** and decrease the release of insulin
- glucagon stimulates glucose synthesis and release by the liver and mobilizes fatty acids from adipose tissue



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During Fasting and Starvation, Metabolism Shifts to Provide Fuel for the Brain

Table 23-5 Available Metabolic Fuels in a Normal-Weight, 70 kg Man and in an Obese, 140 kg Man at the Beginning of a Fast

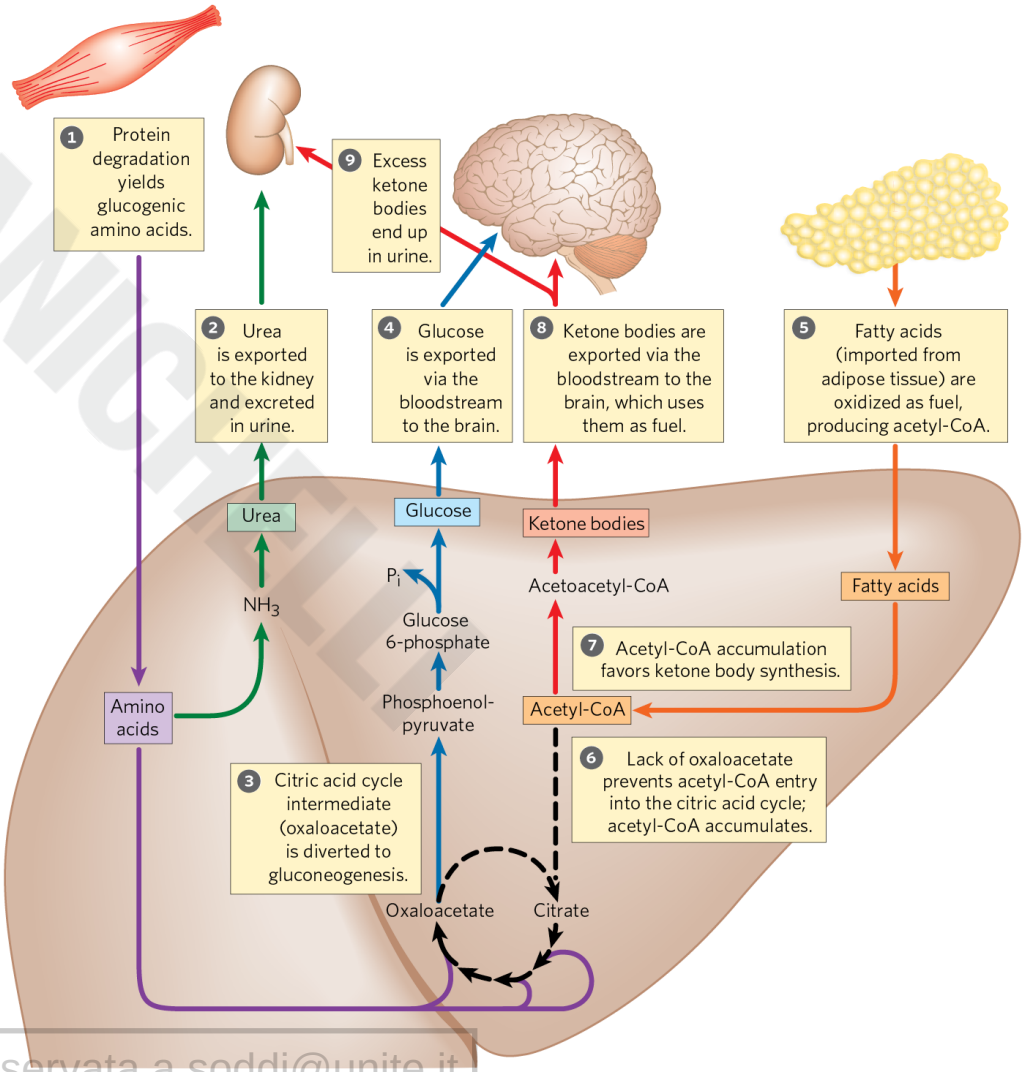
Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival (months)
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	140 (590)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.23	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		165 (690)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	750 (3,100)	
Proteins (mainly muscle)	8	32 (130)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		783 (3,200)	14

P3 Principle 3 (6 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

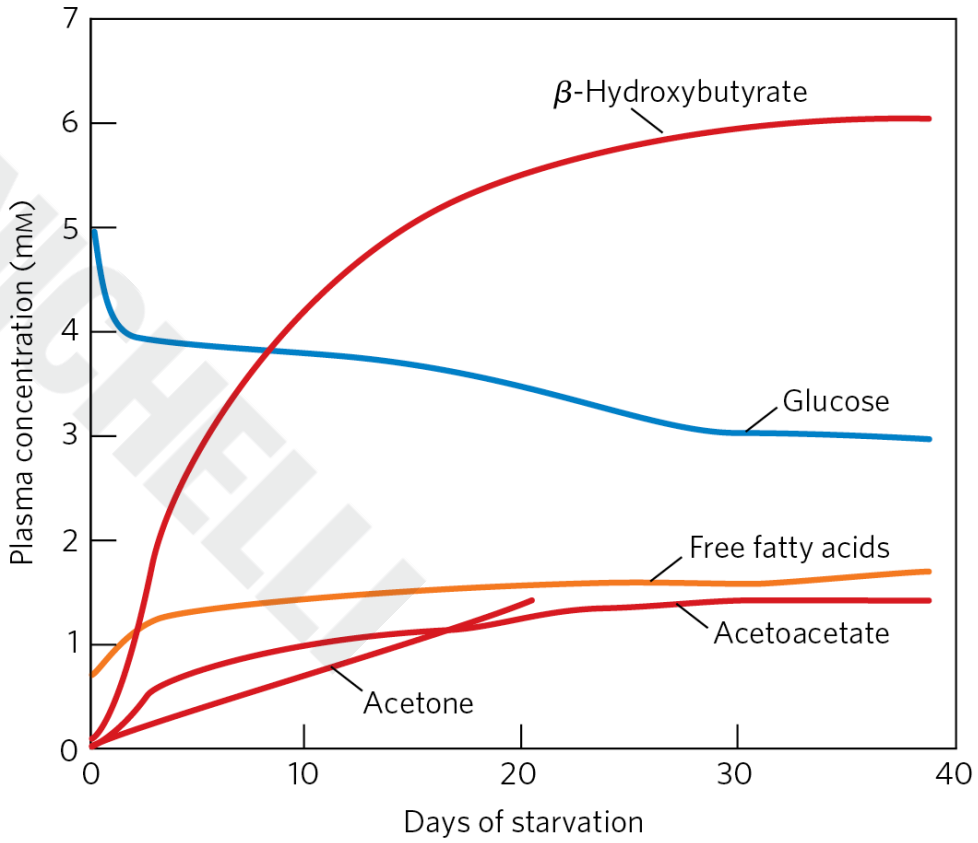
Fuel Metabolism in the Liver During Fasting

- slowing of insulin secretion and increased glucagon secretion mobilize TAGs
- the liver converts fatty acids to ketone bodies for export to other tissues, including the brain



Plasma Concentrations During Starvation

- glucose begins to diminish within 2 days
- levels of ketone bodies rise dramatically after 2 to 4 days
  - exported from the liver to the the heart, skeletal muscle, and brain



Epinephrine Signals Impending Activity

- epinephrine prepares the body for increased activity by mobilizing glucose

TABLE 23-6 Physiological and Metabolic Effects of Epinephrine: Preparation for Action

Immediate effect	Overall effect
Physiological	
↑ Heart rate ↑ Blood pressure ↑ Dilation of respiratory passages	Increase delivery of O_2 to tissues (muscle)
Metabolic	
↑ Glycogen breakdown (muscle, liver) ↓ Glycogen synthesis (muscle, liver) ↑ Gluconeogenesis (liver)	Increase production of glucose for fuel
↑ Glycolysis (muscle)	Increases ATP production in muscle
↑ Fatty acid mobilization (adipose tissue)	Increases availability of fatty acids as fuel
↑ Glucagon secretion ↓ Insulin secretion	Reinforce metabolic effects of epinephrine

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P3 Principle 3 (7 of 7)

Because the brain requires a continuous supply of glucose, maintaining an adequate concentration of glucose in the blood is a high priority in the activities of the other tissues. The liver integrates the use of fuels (glucose, fatty acids, and amino acids) by each tissue to keep the blood glucose level within the optimal range. Hormones carried in the blood (insulin, glucagon, epinephrine, cortisol) mediate this regulation.

Cortisol Signals Stress, Including Low Blood Glucose

- **cortisol** = a glucocorticoid released from the adrenal cortex in response to a variety of stressors (anxiety, fear, pain, low blood glucose, etc.)
  - relatively slow-acting hormone that alters metabolism

Cortisol Acts on Muscle, Liver, and Adipose Tissue

- leads to an increased release of fatty acids from stored TAGs in adipose tissue
- stimulates the breakdown of nonessential muscle proteins and export of amino acids to the liver
- stimulates gluconeogenesis from amino acids and glycerol in the liver
  - raises blood glucose
  - counterbalances the effects of insulin

23.4 Obesity and the Regulation of Body Mass

Body Mass Index (BMI)

- **body mass index (BMI)** = calculated as $\frac{\text{weight in kg}}{\text{height in m}^2}$
  - < 25 is considered normal
  - 25 to 30 is overweight
  - > 30 indicates **obesity**
  - > 40 indicates severe obesity

- obesity increases the likelihood of type 2 diabetes, heart attack, stroke, and cancers of the colon, breast, prostate, and endometrium

P4 Principle 4 (2 of 4)

Maintaining an optimal body mass is an important priority in the adult mammal. Body mass is a function of dietary intake, physical activity, and the choice of metabolic fuel, all of which are subject to hormonal regulation. Hormonal signals between the brain, the adipose tissue, and the gastrointestinal tract help to set activity and feeding behavior.

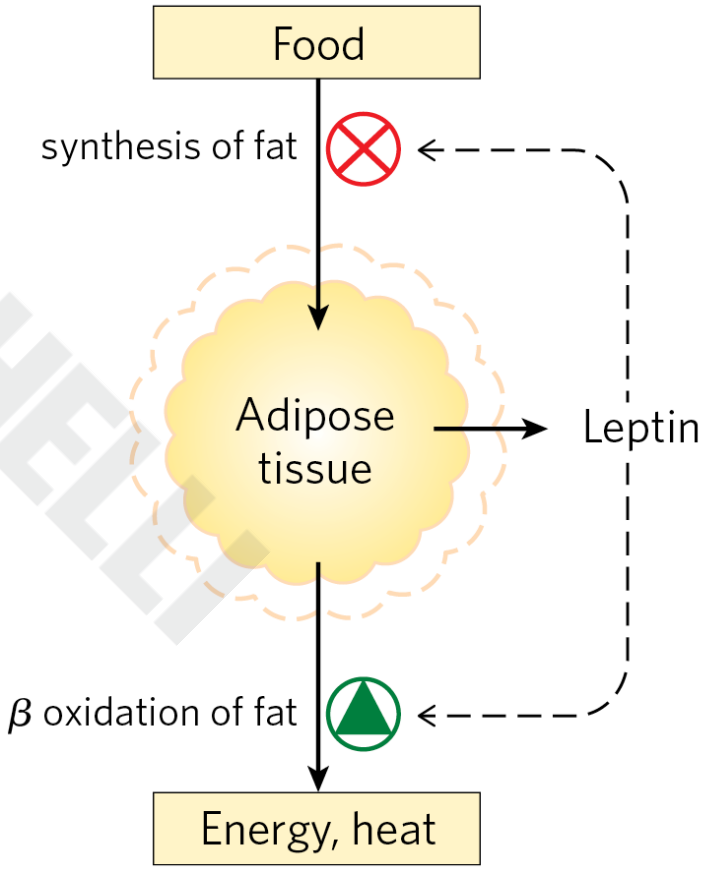
Fates of Excess Dietary Calories

- the body deals with an excess of dietary calories by:
  - converting excess fuel to fat and storing it in adipose tissue
  - burning excess fuel by extra exercise
  - “wasting” fuel by diverting it to heat production (thermogenesis) by uncoupled mitochondria

- in mammals, hormonal and neuronal signals act to keep fuel intake and energy expenditure in balance

Adipose Tissue Has Important Endocrine Functions

- "adiposity negative-feedback" model = suggests that eating behavior is inhibited and energy expenditure is increased whenever body weight exceeds a certain "set point" value



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P4 Principle 4 (3 of 4)

Maintaining an optimal body mass is an important priority in the adult mammal. Body mass is a function of dietary intake, physical activity, and the choice of metabolic fuel, all of which are subject to hormonal regulation. Hormonal signals between the brain, the adipose tissue, and the gastrointestinal tract help to set activity and feeding behavior.

Adipose Tissue Produces Adipokines

- adipose tissue is an important endocrine organ that produces **adipokines** (peptide hormones)
- adipokines may act locally or systemically (endocrine action)
- adipokines carry information about the adequacy of the energy reserves (TAGs) stored in adipose tissue to other tissues and to the brain

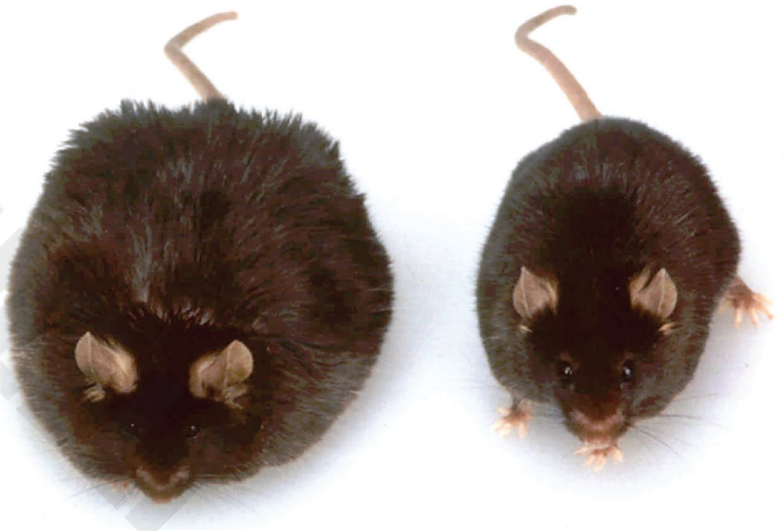
Leptin is an Adipokine

- **leptin** = an adipokine produced by adipose tissue that regulates feeding behavior and energy expenditure to maintain adequate reserves of fat
  - production and release increases with number and size of adipocytes

Obesity Caused by Defective Leptin Production

- mice with two defective copies of the *OB* (obese) gene (*ob*/*ob*) show the behavior and physiology of animals in a constant state of starvation

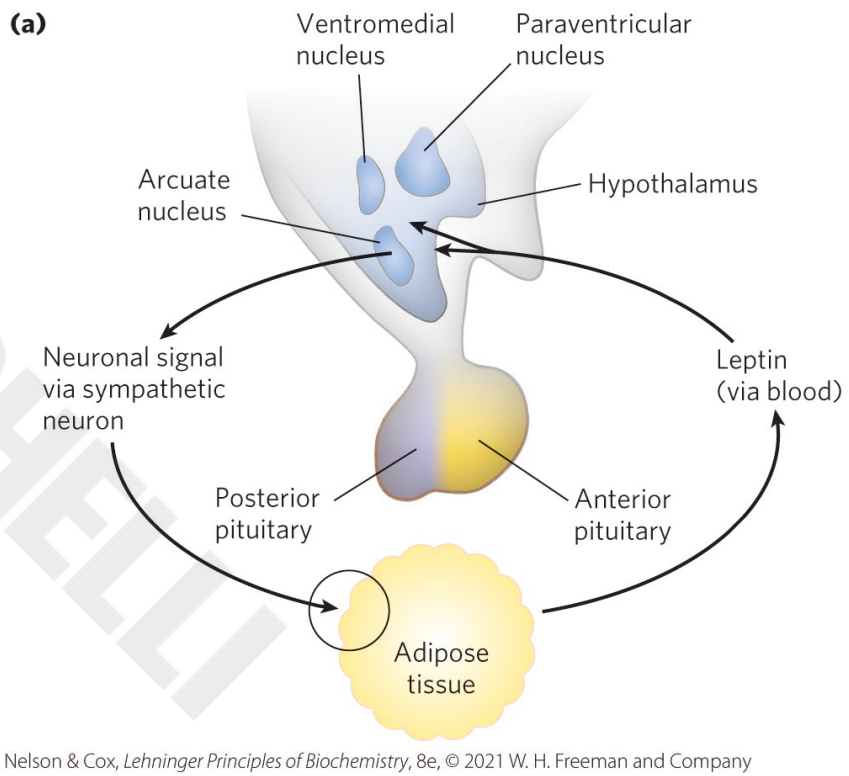
- leptin injections into *ob*/*ob* mice cause the mice to:
  - eat less
  - lose weight
  - increase locomotor activity and thermogenesis



The Rockefeller University/AP Photo.

The Leptin Receptor

- **leptin receptor** = receptor encoded by the *DB* (diabetic) gene that permits signaling by leptin
  - expressed primarily in neurons of the **arcuate nucleus** of the hypothalamus
  - *db*/*db* mice are obese and diabetic



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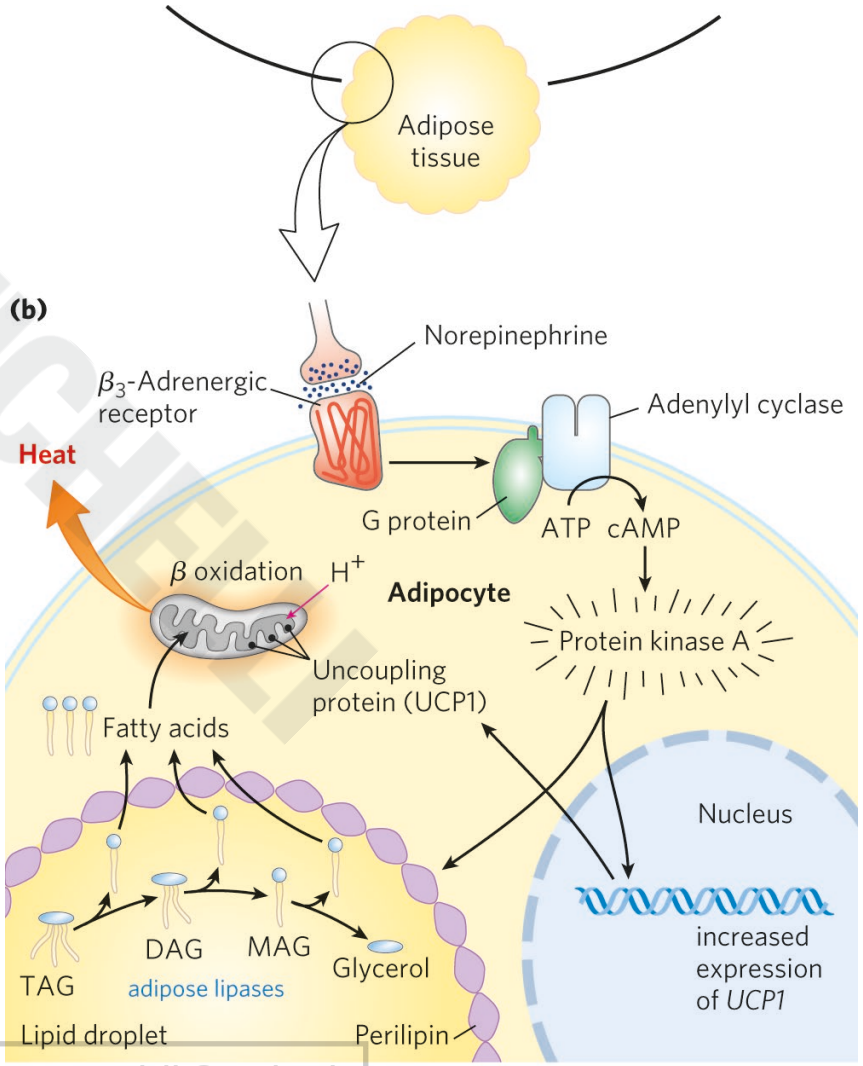
Hypothalamic Regulation of Food Intake and Energy Expenditure

- the hypothalamus responds to leptin with norepinephrine signals to adipocytes
- the signal activates protein kinase A, which triggers fatty acid mobilization and their uncoupled oxidation in mitochondria, generating heat

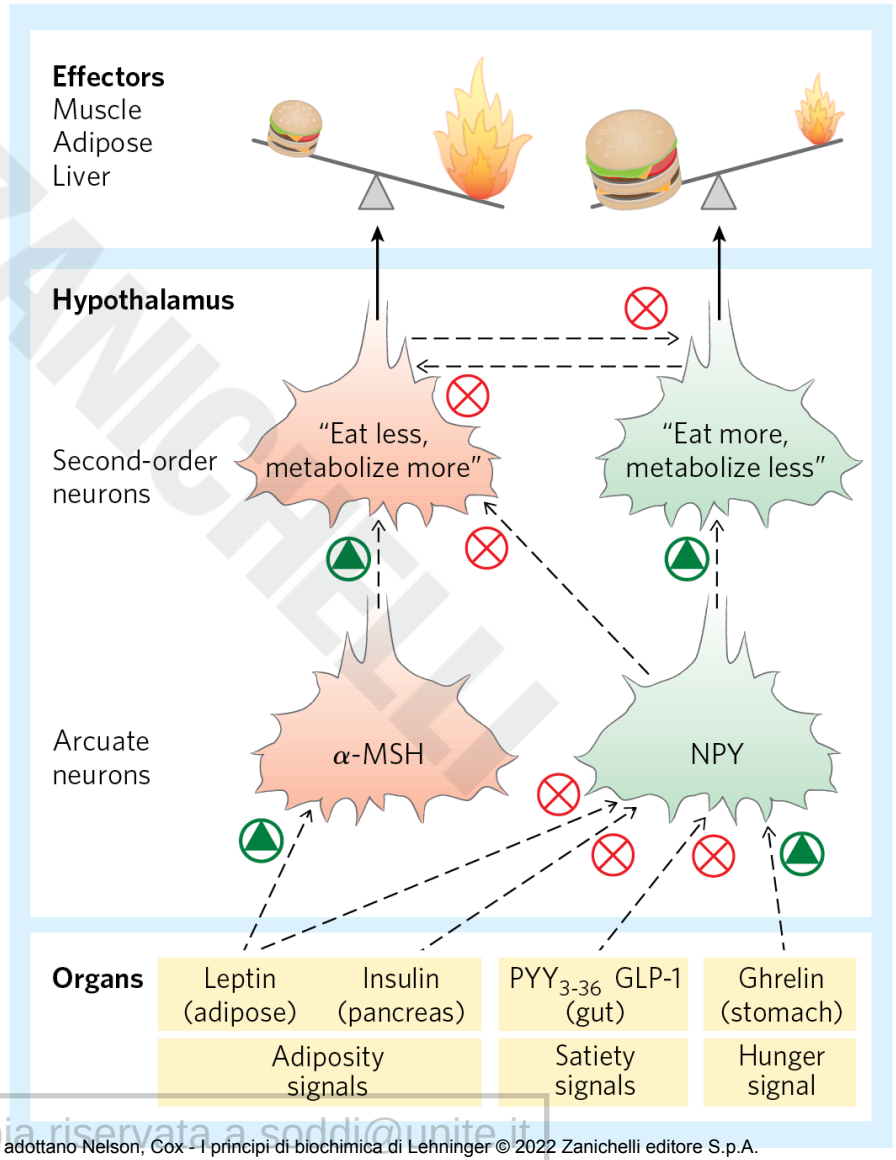


Leptin Stimulates Production of Anorexigenic Peptide Hormones

- two types of neurons in the arcuate nucleus control fuel intake and metabolism:
  - **orexigenic** (appetite-stimulating) neurons stimulate eating by producing and releasing **neuropeptide Y (NPY)**
  - **anorexigenic** (appetite-suppressing) neurons produce ***α*-melanocyte-stimulating hormone** (***α*-MSH**) from its polypeptide precursor POMC

Hormones That Control Eating

- leptin causes the release of anorexigenic peptides, including ***α*-MSH,** to inhibit eating



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Leptin Triggers a Signaling Cascade That Regulates Gene Expression

- leptin receptor monomers dimerize and undergo phosphorylation on several Tyr residues
  - initiates a chain of events that ends with the increased synthesis of the POMC gene

- leptin also:
  - increases synthesis of the mitochondria in brown and beige adipocytes
  - stimulates UCP1 synthesis

Leptin and Human Obesity

- blood levels of leptin are usually much higher in obese animals than in animals of normal body mass

- leptin injections are not effective at reducing weight in individuals that do not have a defective leptin gene (*OB*)
  - indicates some downstream element in the leptin response system is defective in obese individuals

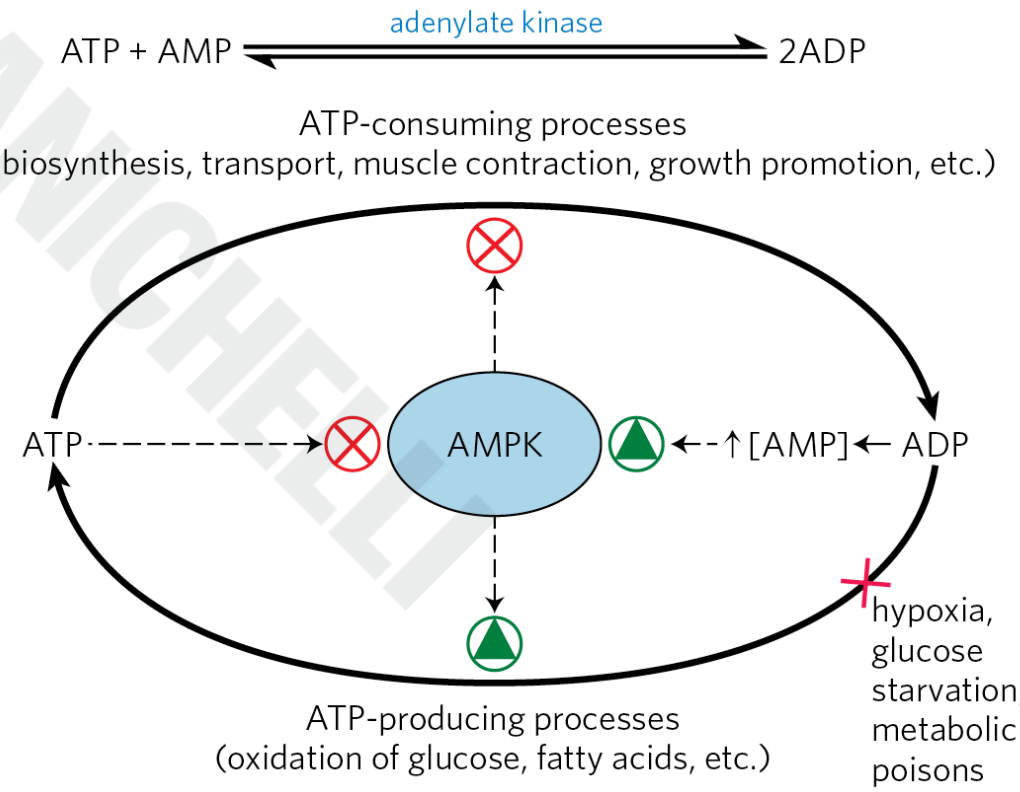
Adiponectin Acts through AMPK to Increase Insulin Sensitivity

- **adiponectin** = an adipokine produced in adipose tissue
  - stimulates fatty acid uptake and oxidation
  - inhibits fatty acid synthesis
  - sensitizes muscle and liver to insulin

- **AMP-activated protein kinase (AMPK)** = mediates many effects of adiponectin

The Role of AMPK in Maintaining Energy Homeostasis

- adiponectin triggers phosphorylation and activation of AMPK
- AMPK is allosterically activated by AMP



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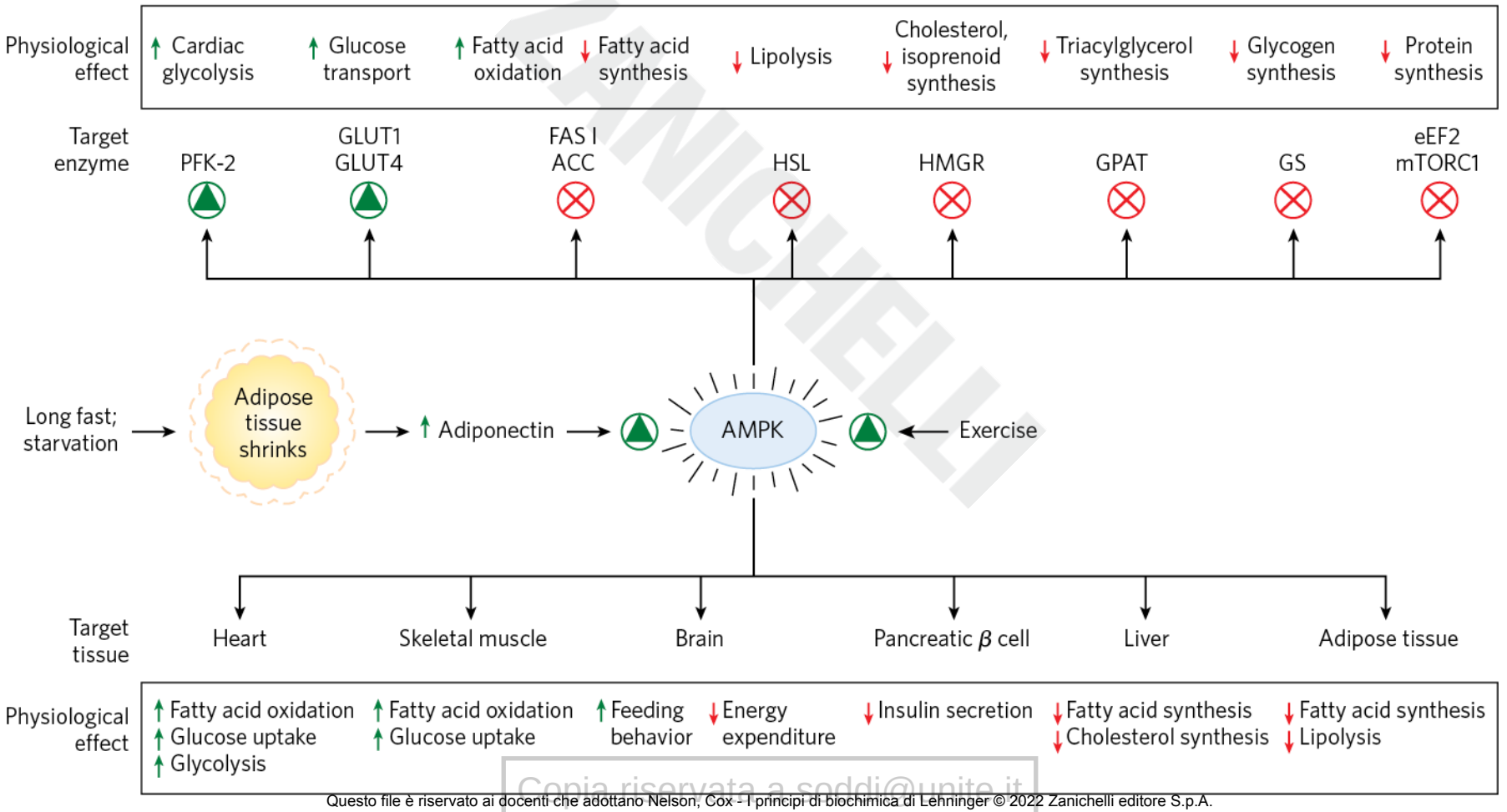
AMPK Coordinates Catabolism and Anabolism in Response to Metabolic Stress



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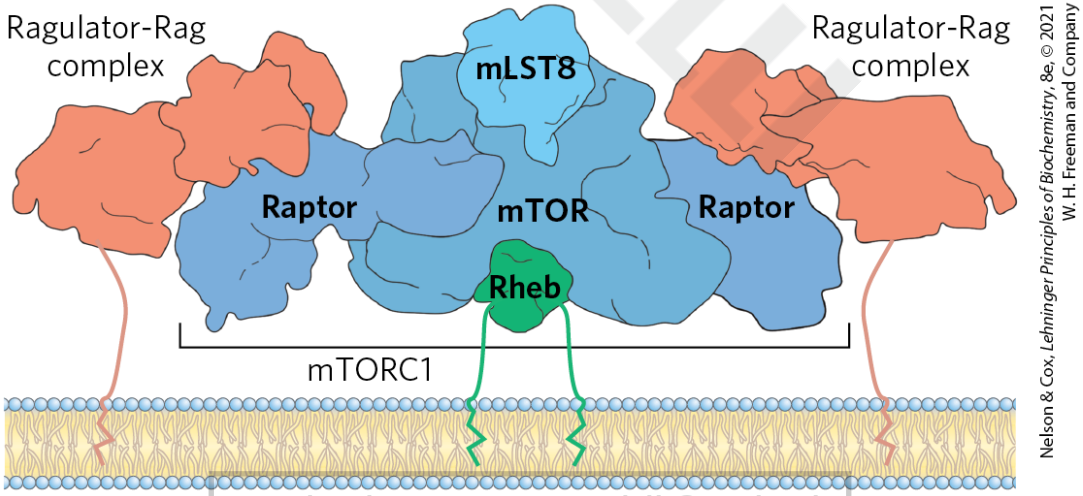
The mTORC1 Pathway Coordinates Cell Growth with the Supply of Nutrients and Energy

- **mTOR** = a highly conserved Ser/Thr kinase
  - forms a complex, **mTORC1**, with a scaffold protein, raptor, and other regulatory proteins
- mTORC is recruited to the cytosolic surface of the lysosome through raptor by the Ragulator-Rag complex
- **Rheb** = G protein that activates the protein kinase activity of mTOR

The mTORC-Ragulator-Rag Complex on the Lysosomal Surface

- the complex integrates signals from inside and outside of the lysosome about:
  - the energy status of the cell
  - the availability of critical amino acids needed for protein synthesis
  - the presence of growth factors



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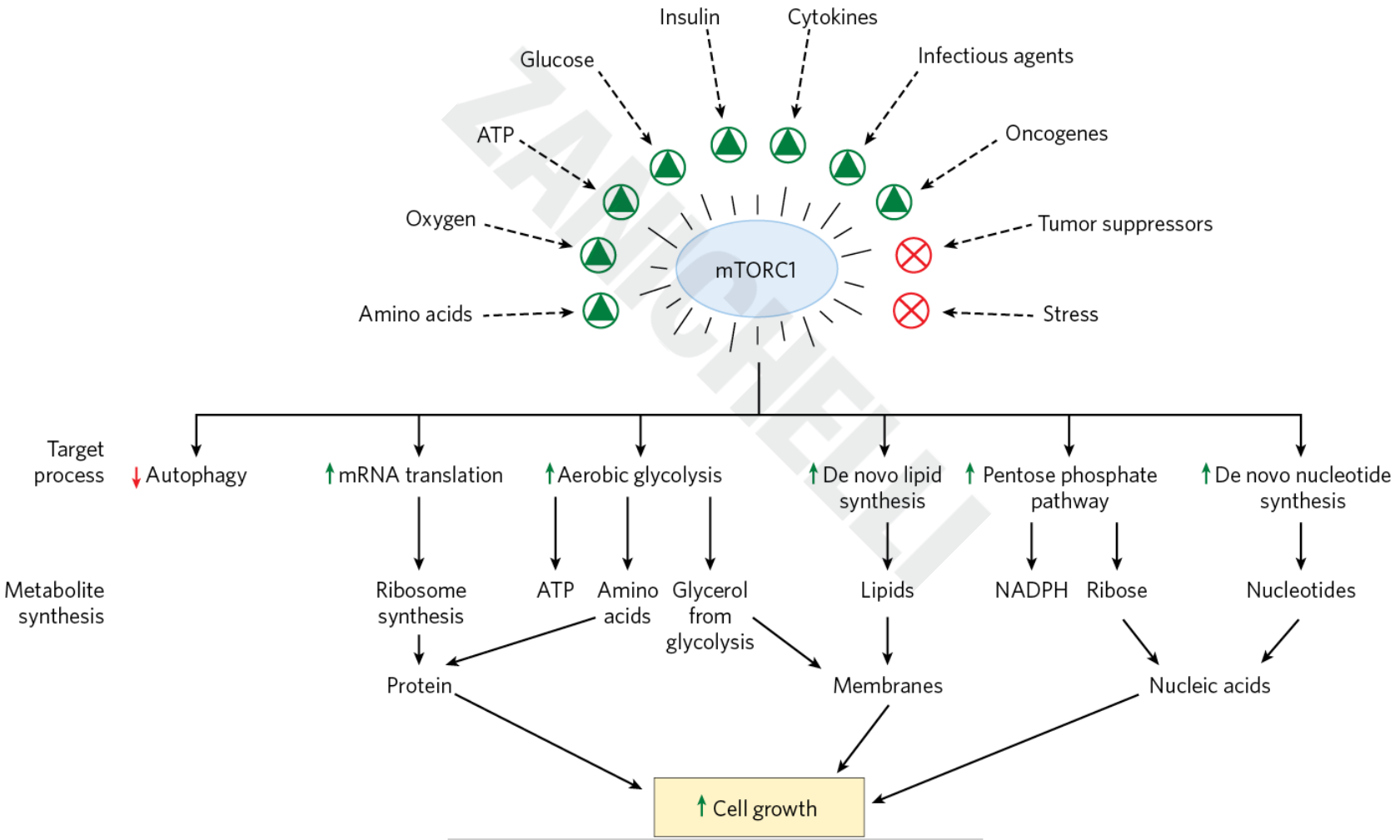
mTORC1 Activation Signals and the Cellular Process it Activates



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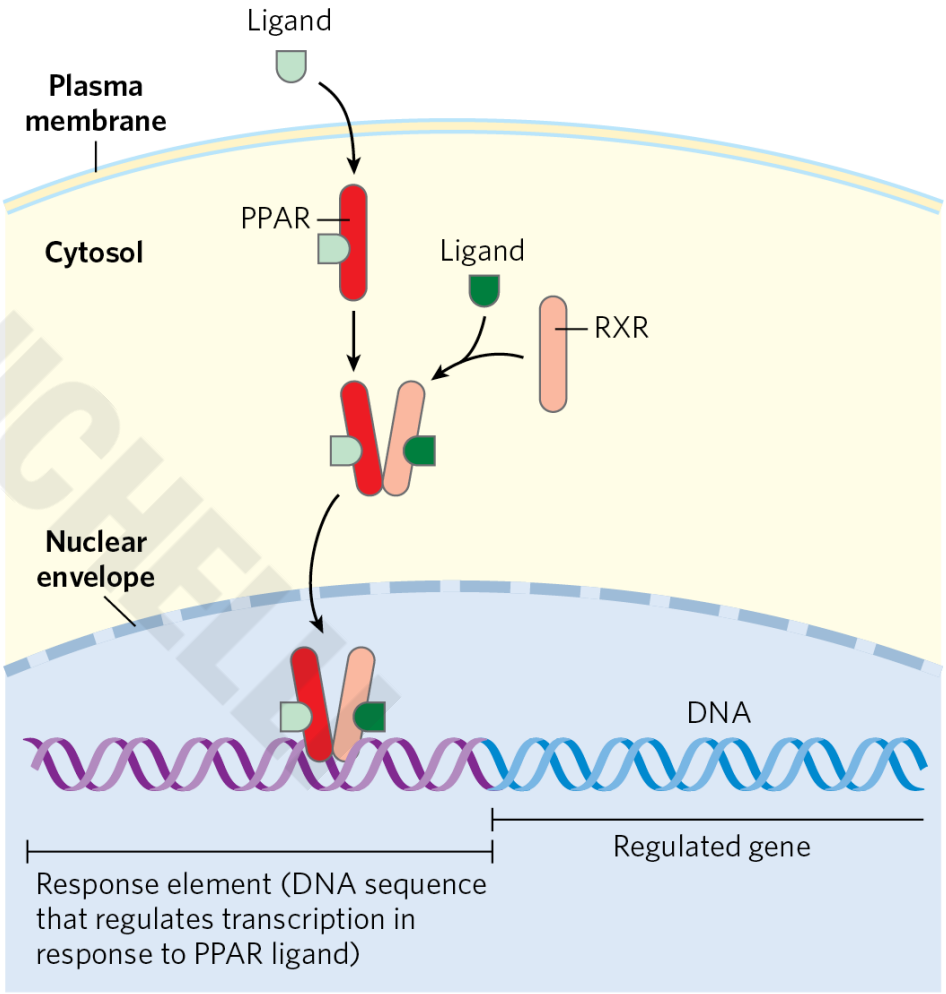
Diet Regulates the Expression of Genes Central to Maintaining Body Mass

- **peroxisome proliferator-activated receptors (PPARs) =** family of ligand-activated transcription factors
  - respond to changes in dietary lipid by altering the expression of genes involved in fat and carbohydrate metabolism

Mode of Action of PPARs

- ligands are fatty acids or fatty acid derivatives
- PPARs form heterodimers in the nucleus with RXR
- the heterodimers bind to regulatory regions of DNA



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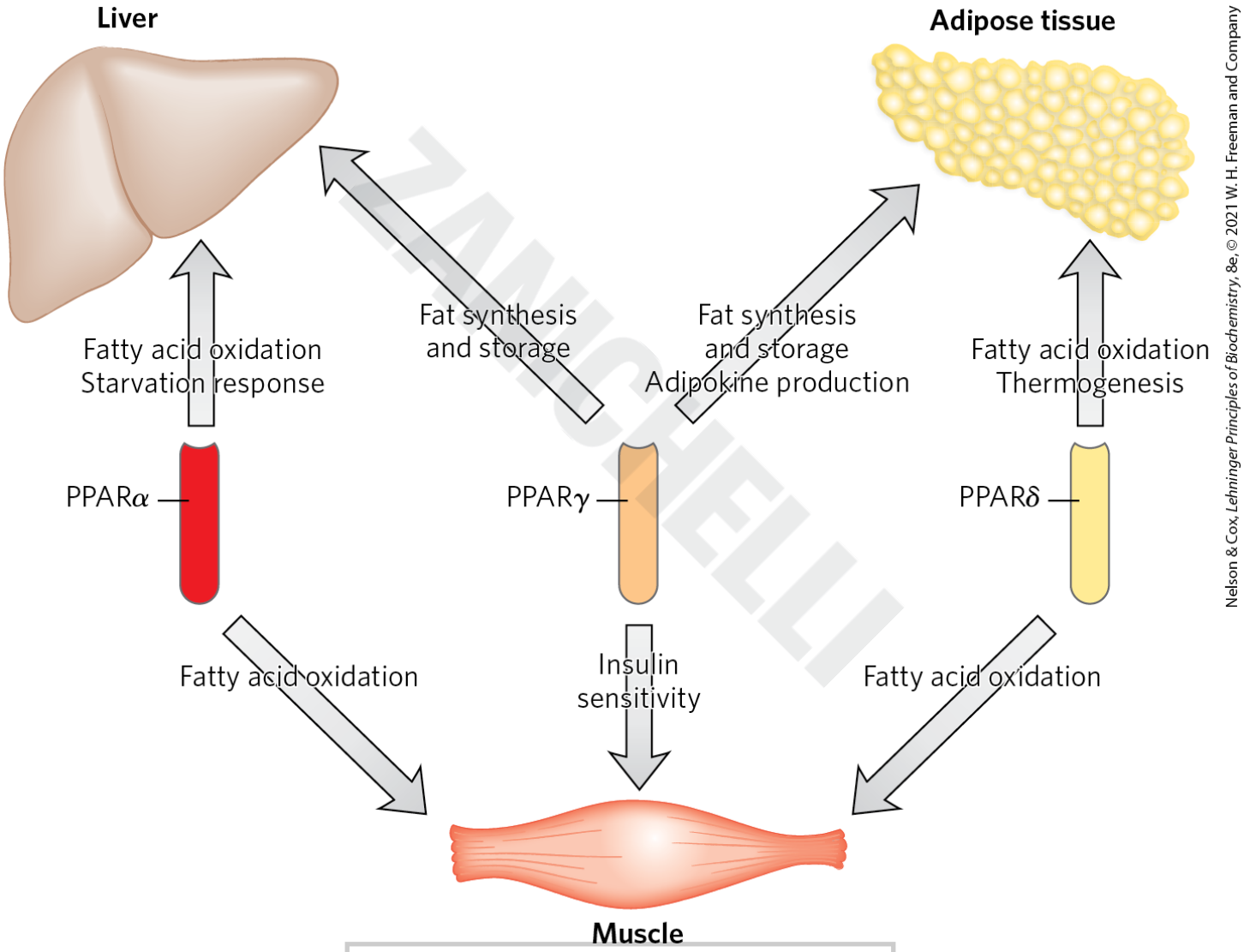
The Three PPAR Isoforms Regulate Lipid and Glucose Homeostasis

- **PPAR*γ*** = regulates the differentiation of fibroblasts into adipocytes and lipid synthesis and storage in adipocytes

- **PPAR*α*** = regulates the uptake and *β* oxidation of fatty acids and the formation of ketone bodies during fasting
  - expressed in liver, kidney, heart, skeletal muscle, and brown adipose tissue

- **PPAR*δ*** = regulates *β* oxidation and energy dissipation through uncoupling of mitochondria
  - acts in the liver and muscle

Metabolic Integration by PPARs



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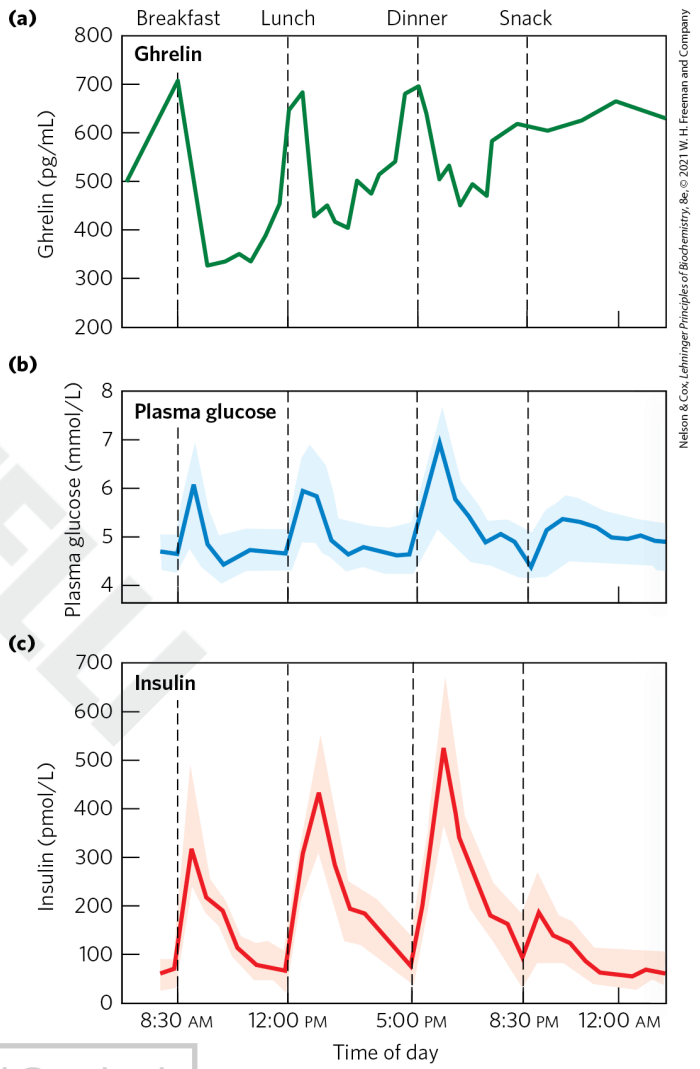
Short-Term Eating Behavior Is Influenced by Ghrelin, PYY_{3-36}, and Cannabinoids

- **ghrelin** = a peptide hormone produced in cells lining the stomach
  - acts on orexigenic (appetite-stimulating) neurons in the arcuate nucleus to produce hunger
  - works on a shorter time scale than leptin and insulin
  - acts through a GPCR to generate IP_3

Variations in Blood Concentrations of Glucose, Ghrelin, and Insulin

- ghrelin concentration in the blood peaks just before a meal
- injection of ghrelin into humans produces immediate sensations of intense hunger



PYY_{3-36} Acts to Lessen Hunger After a Meal

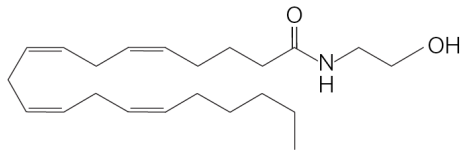
- **PYY_{3-36}** = a peptide hormone secreted by endocrine cells in the small intestine and colon in response to food entering from the stomach
  - acts on orexigenic neurons in the arcuate nucleus to inhibit NPY release and reduce hunger

Cannabinoids

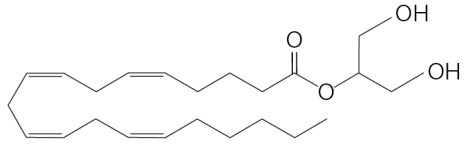
- **endocannabinoids** = eicosanoid lipid messengers that signal the availability of sweet or fatty food and stimulate its consumption
  - act through specific GPCRs in the brain and PNS that control ion channels

- cannabinoid receptors also mediate the psychoactive effects of Δ^9-tetrahydrocannabinol (the main active ingredient in marijuana)

Endocannabinoids

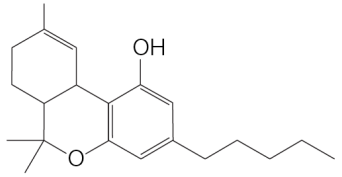


N-Arachidonoylethanolamide (NAE), anandamide

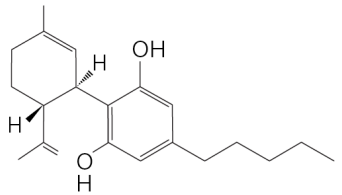


2-Arachidonoylglycerol (2-AG)

Exogenous cannabinoids



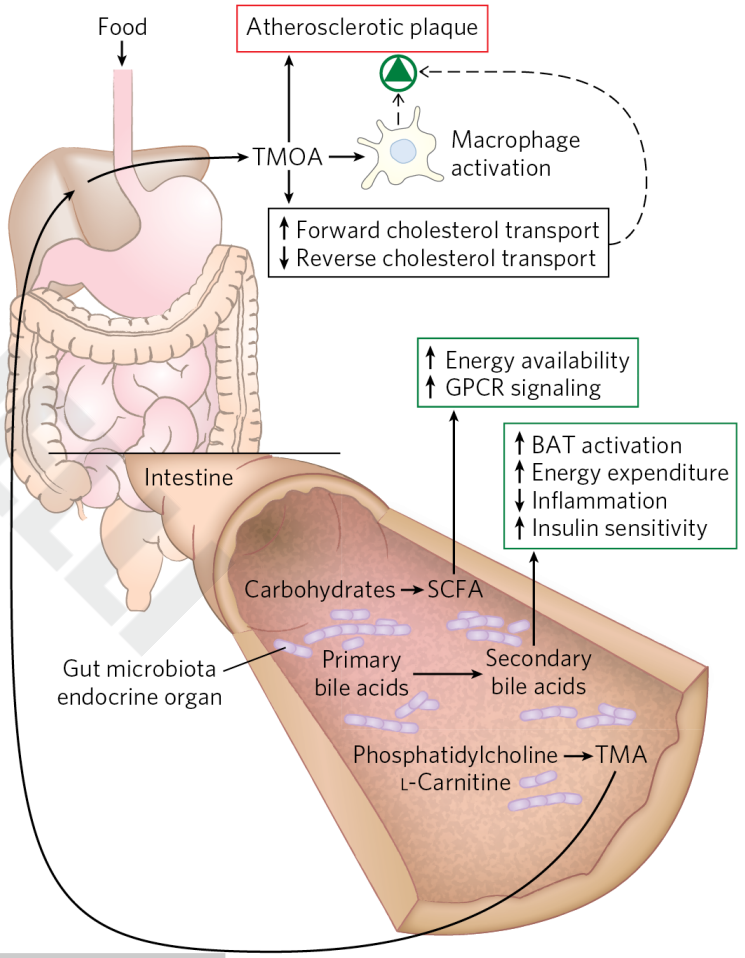
Tetrahydrocannabinol (THC)



Cannabidiol (CBD)

Microbial Symbionts in the Gut Influence Energy Metabolism and Adipogenesis

- Adult humans are hosts to ~10^{14} gut microbes.
- Microbial symbionts in the gut release fermentation products and secondary bile acids.
  - influence release of gut hormones that regulate body mass



Probiotics and Prebiotics

- weight reduction might be accomplished by adding to the gut either:
  - **probiotics** (microbial species that disfavor adipogenesis)
  - **prebiotics** (nutrients that favor the dominance of probiotic microbes)

P4 Principle 4 (4 of 4)

Maintaining an optimal body mass is an important priority in the adult mammal. Body mass is a function of dietary intake, physical activity, and the choice of metabolic fuel, all of which are subject to hormonal regulation. Hormonal signals between the brain, the adipose tissue, and the gastrointestinal tract help to set activity and feeding behavior.

Endocrine Cell Interactions with Gut Microbes May Affect Peptide Release

- endocrine cells in the intestinal tract secrete peptides that modulate food intake and energy expenditure:
  - the anorexigenic $PYY_{3–36}$ and GLP-1
  - the orexigenic ghrelin

- peptide release may be affected by the interaction of endocrine cells with specific microbes in the gut or with their fermentation products

23.5 Diabetes Mellitus

Diabetes Mellitus

- **diabetes mellitus** = a relatively common disease affecting ~9% of the U.S. population

- two major clinical classes of diabetes mellitus:
  - **type 1 diabetes** (insulin-dependent diabetes mellitus (IDDM))
  - **type 2 diabetes** (non-insulin-dependent diabetes mellitus (NIDDM))

Diabetes Mellitus Arises from Defects in Insulin Production or Action

- type 1 diabetes = stems from an autoimmune destruction of pancreatic β cells, resulting in the inability to produce sufficient insulin
  - begins early in life
  - responds to insulin injection

Type 2 Diabetes

- type 2 diabetes = group of diseases in which the regulatory activity of insulin is disordered
  - slower to develop and typically in obese adults
  - responds to insulin injection

Symptoms and Pathology of Diabetes

- both type 1 and type 2 diabetes are characterized by excessive thirst and frequent urination
  - due to excretion of large amounts of glucose in urine

- pathology includes cardiovascular disease, renal failure, blindness, and neuropathy

P5 Principle 5 (2 of 3)

The metabolic activities of cells and organisms are complex and intertwined; perturbation at one point in the system has far-reaching consequences for health. When the normal energy-yielding metabolism of glucose and fatty acids is impeded by defective insulin signaling, the result is the disease diabetes.

Diagnosis of Diabetes

- individuals with type 1 and type 2 diabetes are unable to take up glucose efficiently from the blood

- HbA1c = a glucose derivative of hemoglobin, which forms in the blood and reflects the average blood glucose level

- **glucose-tolerance test** = measures the blood glucose after an overnight fast and after drinking glucose water
  - diabetic individuals assimilate the test dose of glucose poorly and glucose also appears in the urine

Carboxylic Acids (Ketone Bodies) Accumulate in the Blood of Those with Untreated Diabetes

- because glucose is unavailable to cells, fatty acids become the principal fuel

- this leads to excessive but incomplete oxidation of fatty acids in the liver
  - high [NADH]/[NAD^+] ratio produced by β oxidation inhibits the cycle
  - acetyl-CoA accumulates

Untreated Diabetes Can Cause Ketoacidosis

- accumulated acetyl-CoA leads to **ketosis** (the overproduction of ketone bodies)
  - results in greatly increased concentrations of ketone bodies in the blood (ketonemia) and urine (ketonuria)

- ionization of ketone bodies can lead to **acidosis** (a lowering of blood pH)

- **ketoacidosis** = the potentially life-threatening condition of ketosis and acidosis

P5 Principle 5 (3 of 3)

The metabolic activities of cells and organisms are complex and intertwined; perturbation at one point in the system has far-reaching consequences for health. When the normal energy-yielding metabolism of glucose and fatty acids is impeded by defective insulin signaling, the result is the disease diabetes.

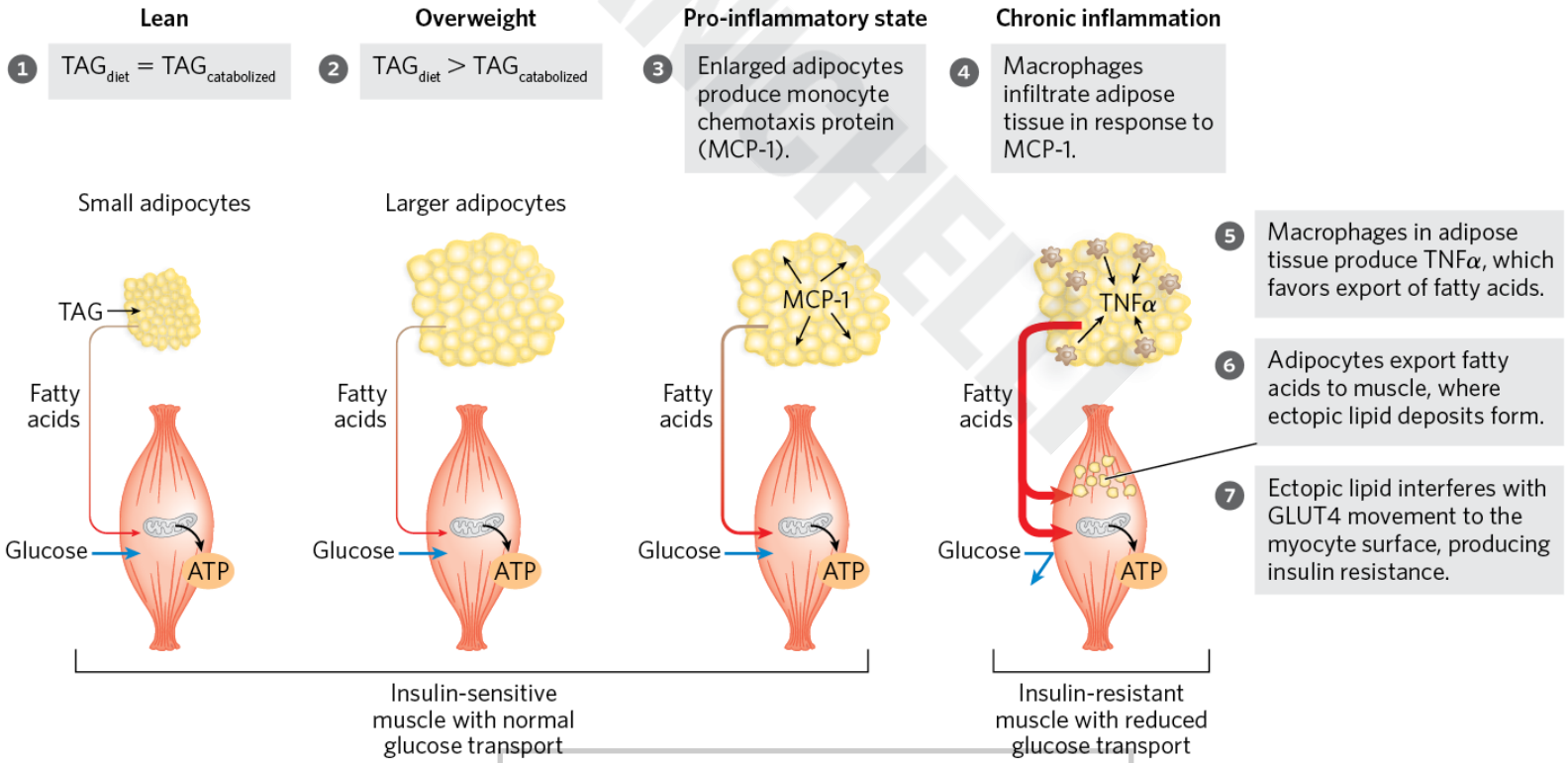
In Type 2 Diabetes the Tissues Become Insensitive to Insulin

- a hallmark of **type 2 diabetes** is the development of insulin resistance
  - more insulin is required to bring about the same biological effects

- **metabolic syndrome** = the stage preceding type 2 diabetes
  - includes obesity, hypertension, abnormal blood lipids, high fasting blood glucose, and reduced ability to clear glucose
  - affects ~30% of the adult U.S. population

The “Lipid Toxicity” Hypothesis

- insulin resistance in type 2 diabetes may be due to abnormal lipid storage in muscle and liver when adipocytes cannot store additional TAGs



Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

Type 2 Diabetes Is Managed with Diet, Exercise, Medication, and Surgery

Table 23-7 Treatments for Type 2 Diabetes Mellitus

Intervention/treatment	Direct target	Effect of treatment
Weight loss	Adipose tissue; reduction in TAG content	Reduces lipid burden; increases capacity for lipid storage in adipose tissue; restores insulin sensitivity
Exercise	AMPK, activated by increasing [AMP]/[ATP]	Aids weight loss (see Fig. 23-34)
Bariatric surgery	Unknown	Leads to weight loss, better control of blood glucose
Sulfonylureas: glipizide (Glucotrol), glyburide (Micronase), glimepiride (Amaryl)	Pancreatic β cells; K^+ channels blocked	Stimulates insulin secretion by pancreas (see Fig. 23-24)
Biguanides: metformin (Glucophage)	AMPK, activated	Increases glucose uptake by muscle; decreases glucose production in liver
Thiazolidinediones: rosiglitazone (Avandia), pioglitazone (Actos)	PPARγ	Stimulates expression of genes potentiating the action of insulin in liver, muscle, adipose tissue; increases glucose uptake; decreases glucose synthesis in liver
GLP-1 modulators: exenatide (Byetta), sitagliptin (Januvia), dulaglutide (Trulicity)	Glucagon-like peptide-1, dipeptide protease IV	Enhances insulin secretion by pancreas

Irisin

- **irisin** = increases the expression of *UCP1* genes in white adipose tissue and stimulates the development of beige adipocytes
  - exercise increases release from muscle into the blood