- **Hormones** are small molecules or proteins that are produced in one tissue, released into the bloodstream, and carried to other tissues, where they act through specific receptors to bring about changes in cellular activities.

- We also include in this discussion short-lived signals such as NO, which acts locally, on neighboring cells.

- Hormones serve to coordinate the metabolic activities of several tissues or organs.

- Virtually every process in a complex organism is regulated by one or more hormones: maintenance of blood pressure, blood volume, and electrolyte balance; embryogenesis; sexual differentiation, development, and reproduction; hunger, eating behavior, digestion, and fuel allocation—to name but a few.

- We examine here the methods for detecting and measuring hormones and their interaction with receptors, and we consider a representative selection of hormone types.

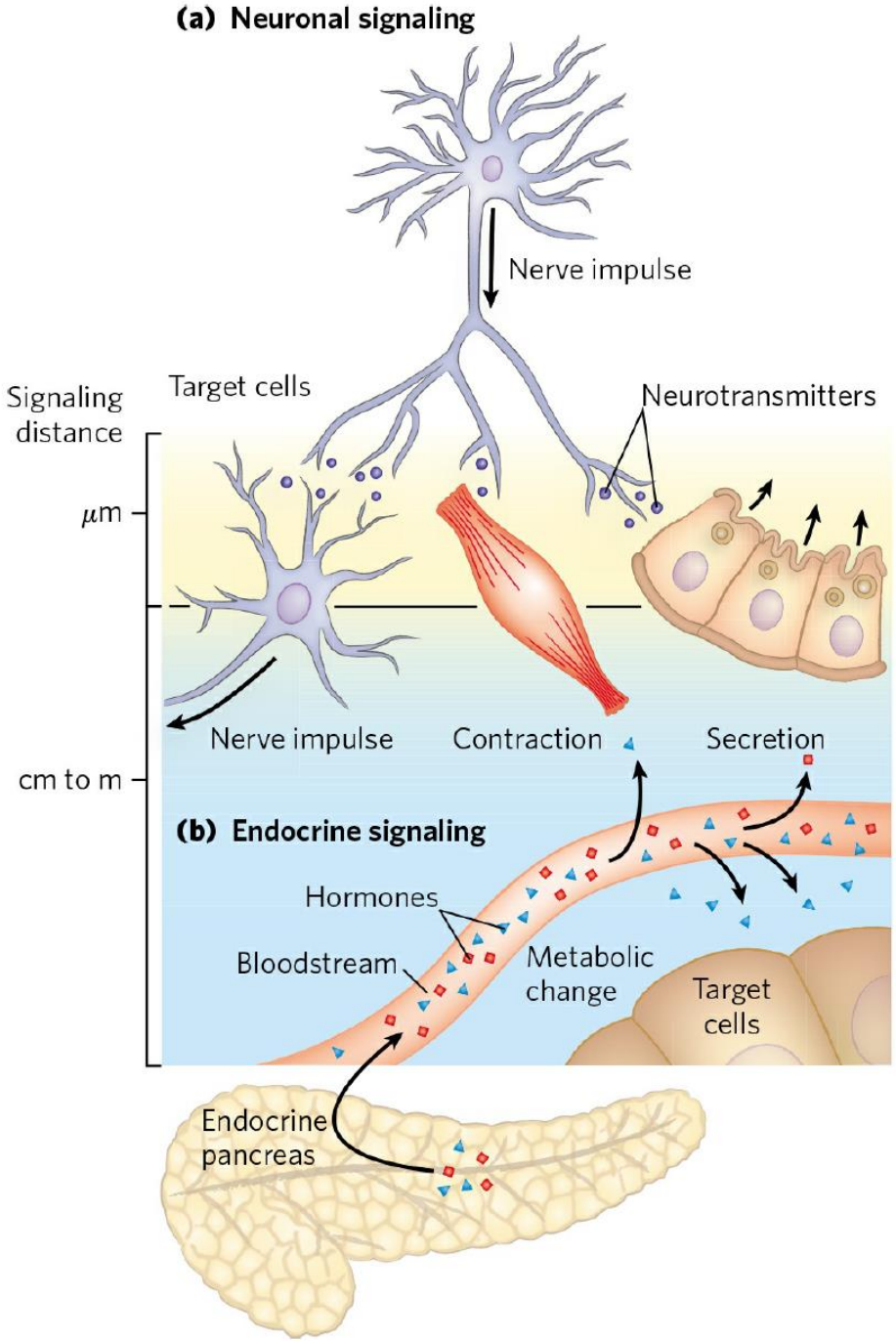
- The coordination of metabolism in mammals is achieved by the **neuroendocrine system**.

- Individual cells in one tissue sense a change in the organism's circumstances and respond by secreting a chemical messenger that passes to another cell in the same or different tissue, where the messenger binds to a receptor molecule and triggers a change in this target cell.

- These chemical messengers may relay information over very short or very long distances.

- In neuronal signaling, the chemical messenger is a neurotransmitter (acetylcholine, for example) and may travel only a fraction of a micrometer, across a synaptic cleft to the next neuron in a network.

- In hormonal signaling, the messengers—hormones—are carried in the bloodstream to neighboring cells or to distant organs and tissues; they may travel a meter or more before encountering their target cell.


(a) Neuronal signaling
Nerve impulse
Signaling distance
Target cells
Neurotransmitters
μm
Nerve impulse
Contraction
Secretion
cm to m
(b) Endocrine signaling
Hormones
Bloodstream
Metabolic change
Target cells
Endocrine pancreas

- Except for this anatomic difference, these two chemical signaling mechanisms are remarkably similar, and the same molecule can sometimes act as both neurotransmitter and hormone.

- Epinephrine and norepinephrine, for example, serve as neurotransmitters at certain synapses of the brain and at neuromuscular junctions of smooth muscle and as hormones that regulate fuel metabolism in liver and muscle.

- The following discussion of cellular signaling emphasizes hormone action, drawing on discussions of fuel metabolism in earlier chapters, but most of the fundamental mechanisms described here also occur in neurotransmitter action.

- How is a hormone detected and isolated?

- First, researchers find that a physiological process in one tissue depends on a signal that originates in another tissue.

- Insulin, for example, was first recognized as a substance that is produced in the pancreas and affects the concentration of glucose in blood and urine .

- Once a physiological effect of the putative hormone is discovered, a quantitative bioassay for the hormone can be developed.

- In the case of insulin, the assay consisted of injecting extracts of pancreas (a crude source of insulin) into experimental animals deficient in insulin, then quantifying the resulting changes in glucose concentration in blood and urine.

- To isolate a hormone, the biochemist fractionates extracts containing the putative hormone, with the same techniques used to purify other biomolecules (solvent fractionation, chromatography, and electrophoresis), and then assays each fraction for hormone activity.

- Once the chemical has been purified, its composition and structure can be determined.

- This protocol for hormone characterization is deceptively simple.

- Hormones are extremely potent and are produced in very small amounts.

- Obtaining sufficient quantities of a hormone to allow its chemical characterization often requires biochemical isolations on a heroic scale.

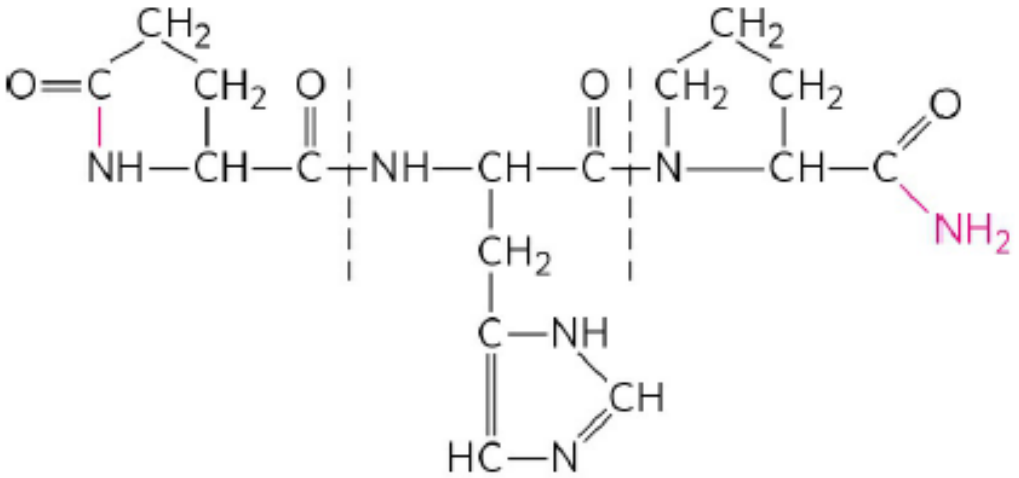
- When Andrew Schally and Roger Guillemin independently purified and characterized thyrotropin-releasing hormone (TRH) from the hypothalamus, Schally's group processed about 20 tons of hypothalamus from nearly two million sheep, and Guillemin's group extracted the hypothalamus from about a million pigs.

- TRH proved to be a simple derivative of the tripeptide Glu–His–Pro).

- Once the structure of the hormone was known, it could be chemically synthesized in large quantities for use in physiological and biochemical studies.

- For their work on hypothalamic hormones, Schally and Guillemin shared the Nobel Prize in Physiology or Medicine in 1977, along with Rosalyn Yalow, who (with Solomon A. Berson) developed the extraordinarily sensitive radioimmunoassay (RIA) for peptide hormones and used it to study hormone action.

❖ This technique revolutionized hormonere search by making possible the rapid, quantitative, and specific measurement of hormones in minute amounts.



pyroGlu-His-Pro-NH_2

FIGURE 23-2 The structure of thyrotropin-releasing hormone (TRH). Purified (through heroic efforts) from extracts of hypothalamus, TRH proved to

- Hormone-specific antibodies are the key to RIA and its modern equivalent, the enzyme-linked immunosorbent assay (ELISA).

- Purified hormone, injected into rabbits, mice, or chickens, elicits antibodies that bind to the hormone with very high affinity and specificity.

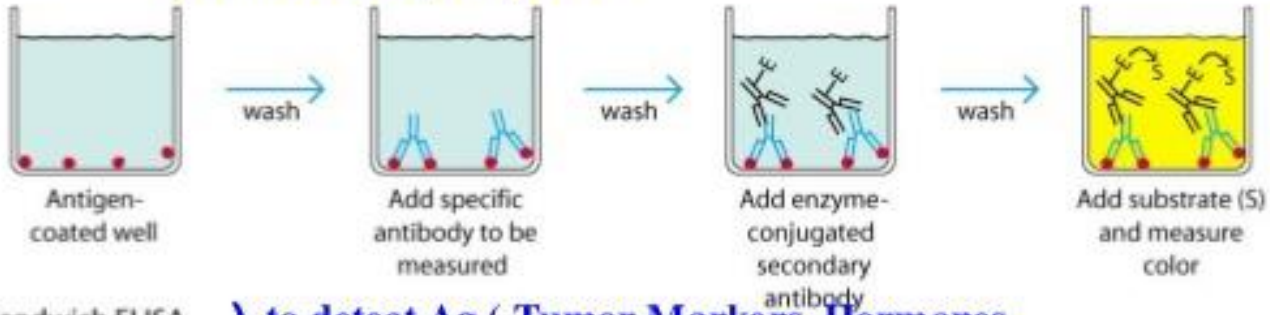
- These antibodies may be purified and either radioisotopically labeled (for RIA) or conjugated with an enzyme that produces a colored product (for ELISA).

- The tagged antibodies are then allowed to interact with extracts containing the hormone.

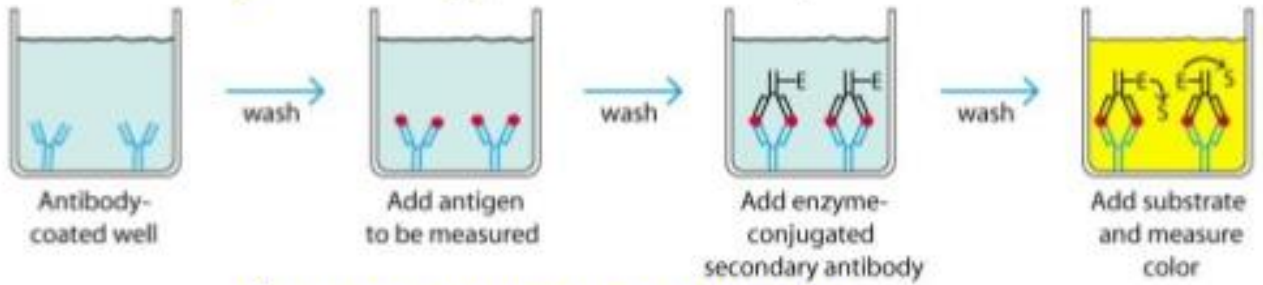
- The fraction of antibody bound by the hormone in the extract is quantified by radiation detection or photometry.

- Because of the high affinity of the antibody for the hormone, such assays can be made sensitive to picograms of hormone in a sample.

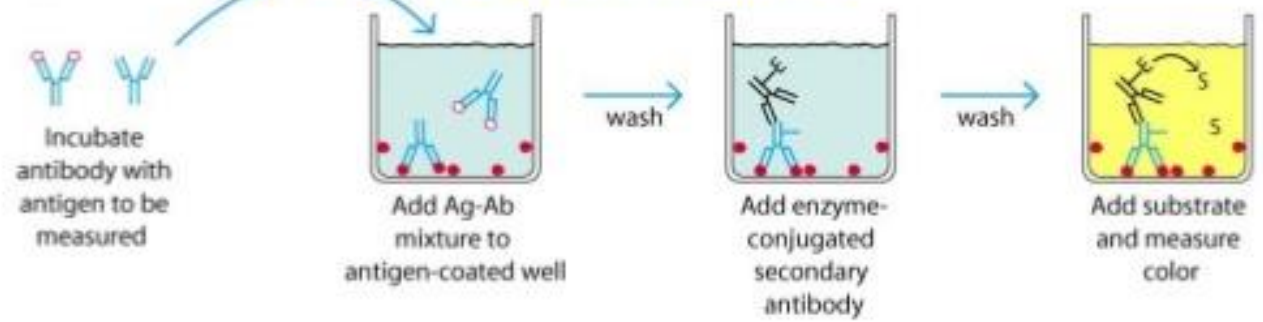
(a) Indirect ELISA)to detect Ab (HIV, HCV



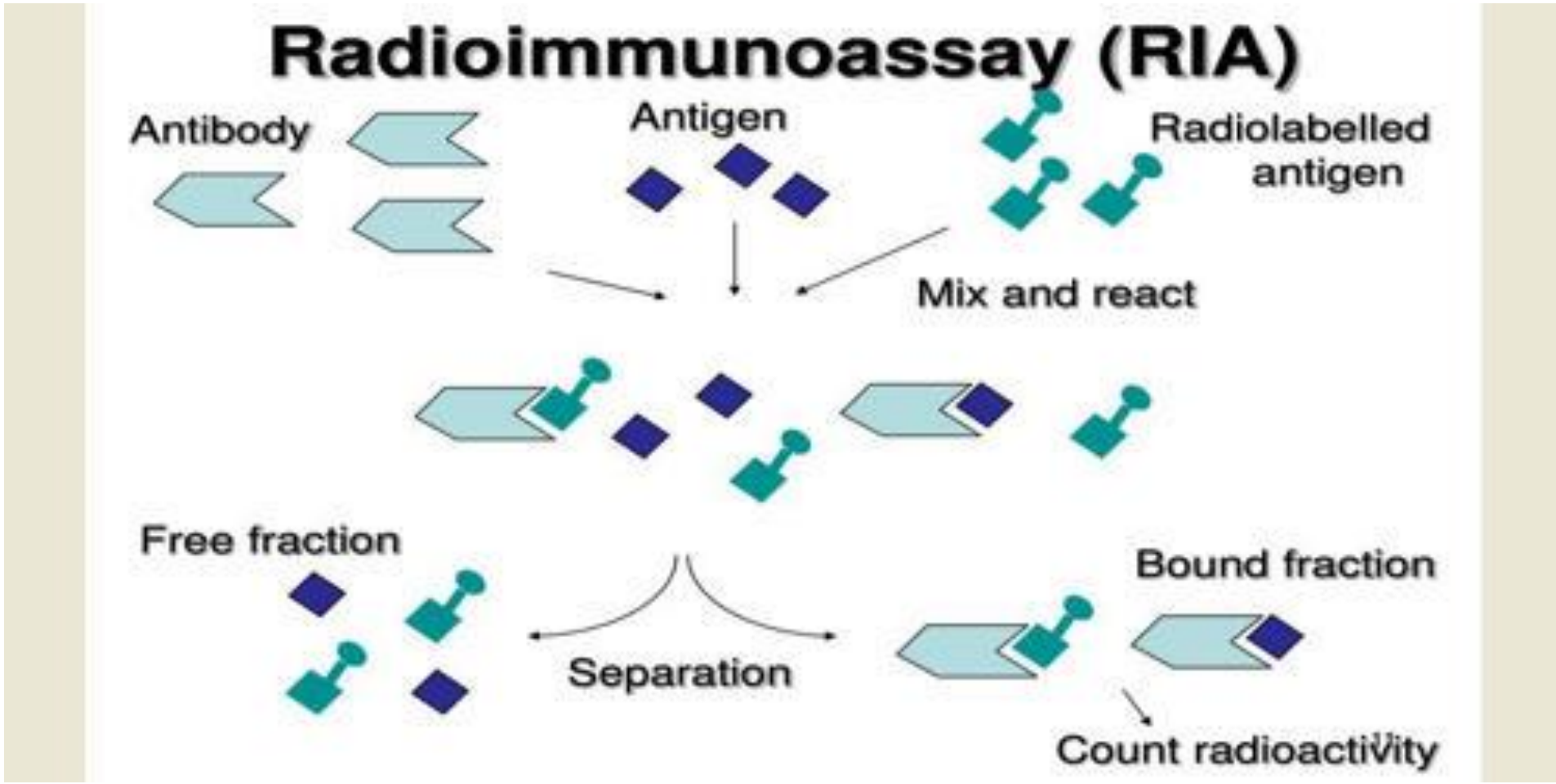
(b) Sandwich ELISA) to detect Ag (Tumor Markers, Hormones



(c) Competitive ELISA) to detect Ag (Free Testosterone



Comparison between Indirect Sandwich & Competitive ELISA


Radioimmunoassay (RIA)
Antibody
Antigen
Radiolabelled antigen
Mix and react
Free fraction
Separation
Bound fraction
Count radioactivity

- All hormones act through highly specific receptors in hormone-sensitive target cells, to which the hormones bind with high affinity.

- Each cell type has its own combination of hormone receptors, which define the range of its hormone responsiveness.

- Moreover, two cell types with the same type of receptor may have different intracellular targets of hormone action and thus may respond differently to the same hormone.

- The specificity of hormone action results from structural complementarity between the hormone and its receptor; this interaction is extremely selective, so even structurally similar hormones can have different effects if they preferentially bind to different receptors.

- The high affinity of the interaction allows cells to respond to very low concentrations of hormone.

- In the design of drugs intended to intervene in hormonal regulation, we need to know the relative specificity and affinity of the drug and the natural hormone.

- The intracellular consequences of ligand-receptor interaction are of at least four general types:

- (1) a second messenger, such as cAMP, cGMP, or inositol trisphosphate, generated inside the cell acts as an allosteric regulator of one or more enzymes;

- (2) a receptor tyrosine kinase is activated by the extracellular hormone;

- (3) a change in membrane potential results from the opening or closing of a hormone-gated ion channel; and

- (4) a steroid or steroid-like molecule causes a change in the level of expression (transcription of DNA into mRNA) of one or more genes, mediated by a nuclear hormone receptor protein.

- Water-soluble peptide and amine hormones, such as insulin and epinephrine, act extracellularly by binding to cell surface receptors that span the plasma membrane.

- When the hormone binds to its extracellular domain, the receptor undergoes a conformational change analogous to that produced in an allosteric enzyme by binding of an effector molecule.

- The conformational change triggers the effect of the hormone.

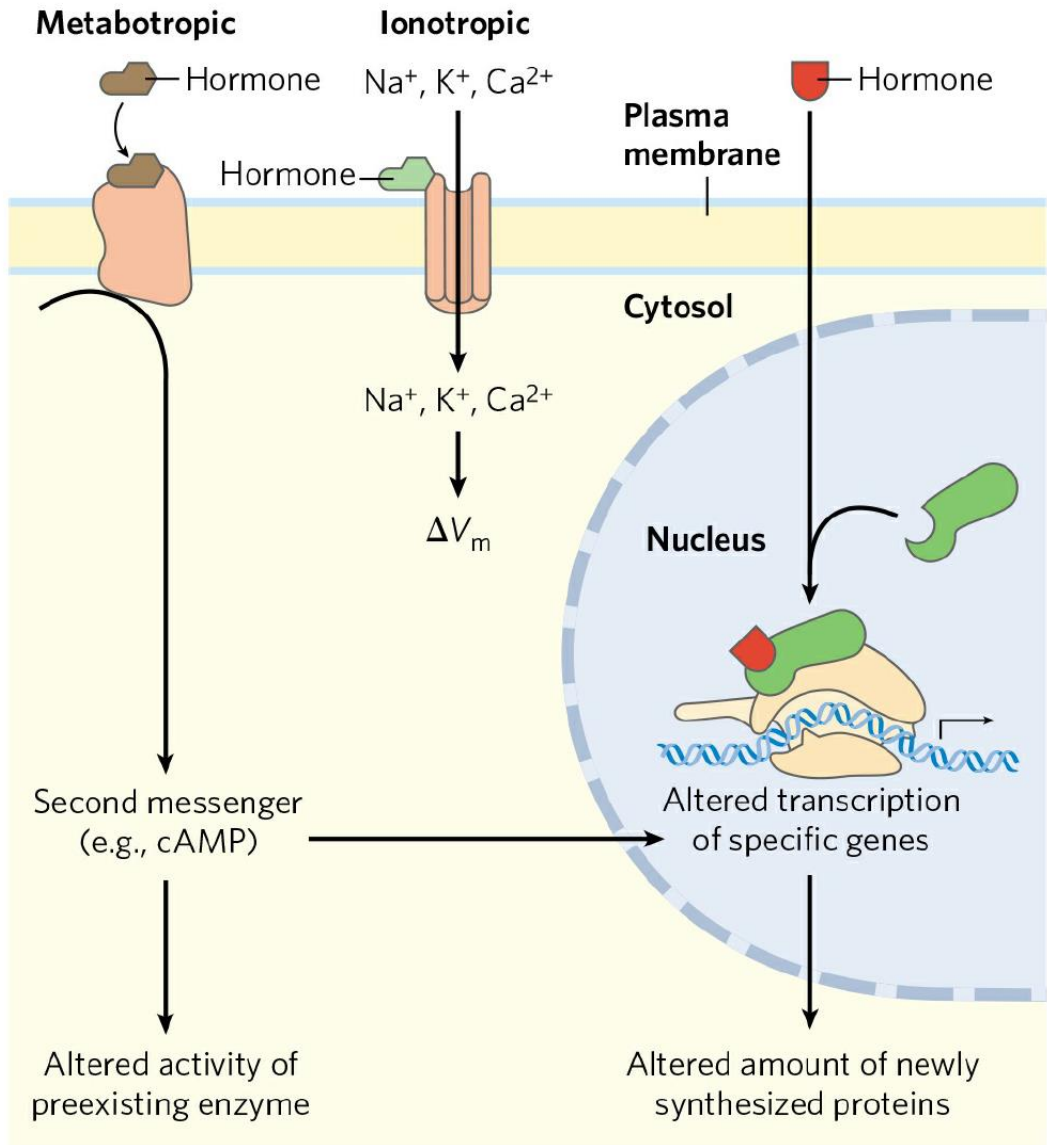
- With metabotropic receptors, the change activates or inhibits an enzyme downstream from the receptor; with ionotropic receptors, an ion channel in the plasma membrane opens or closes, resulting in a change in membrane potential or in the concentration of an ion such as Ca^{2+}.

Cell surface receptor

Peptide or amine hormone binds to receptor on the outside of the cell; acts through receptor without entering the cell.

Nuclear receptor

Steroid or thyroid hormone enters the cell; hormone-receptor complex acts in the nucleus.



- A single hormone molecule, in forming a hormone-receptor complex, activates a catalyst that produces many molecules of second messenger, so the receptor serves as both signal transducer and signal amplifier.

- The signal may be further amplified by a signaling cascade, a series of steps in which a catalyst (such as a protein kinase) activates another catalyst (another protein kinase), resulting in very large amplifications of the original signal.

- A cascade of this type occurs in the regulation of glycogen synthesis and breakdown by epinephrine.

- Epinephrine activates (through its receptor) adenylyl cyclase, which produces many molecules of cAMP for each molecule of receptor-bound hormone.

- Cyclic AMP in turn activates cAMP-dependent protein kinase (protein kinase A), which activates glycogen phosphorylase b kinase, which activates glycogen phosphorylase b.

- The result is signal amplification: one epinephrine molecule causes the production of many thousands or millions of molecules of glucose 1-phosphate from glycogen.

- Water-insoluble hormones, including the steroid, retinoid, and thyroid hormones, readily pass through the plasma membrane of their target cells to reach their receptor proteins in the nucleus.

- The hormone-receptor complex itself carries the message: it interacts with DNA to alter the expression of specific genes, changing the enzyme complement of the cell and thereby changing cellular metabolism.

- Hormones that act through plasma membrane receptors generally trigger very rapid physiological or biochemical responses.

- Just seconds after the adrenal medulla secretes epinephrine into the bloodstream, skeletal muscle responds by accelerating the breakdown of glycogen.

- By contrast, the thyroid hormones and the sex (steroid) hormones promote maximal responses in their target tissues only after hours or even days.

- These differences in response time correspond to different modes of action. In general, the fast-acting hormones lead to a change in the activity of one or more pre-existing enzymes in the cell, by allosteric mechanisms or covalent modification.

- The slower-acting hormones generally alter gene expression, resulting in the synthesis of more (upregulation) or less (downregulation) of the regulated protein(s).

- Mammals have several classes of hormones, distinguishable by their chemical structures and their modes of action.

- Peptide, catecholamine, and eicosanoid hormones act from outside the target cell via cell surface receptors.

- Steroid, vitamin D, retinoid, and thyroid hormones enter the cell and act through nuclear receptors.

- Nitric oxide (a gas) also enters the cell, but activates a cytosolic enzyme, guanylyl cyclase.

- Hormones can also be classified by the way they get from their point of release to their target tissue.

- Endocrine hormones are released into the blood and carried to target cells throughout the body (insulin and glucagon are examples).

- Paracrine hormones are released into the extracellular space and diffuse to neighboring target cells (the eicosanoid hormones are of this type).

- Autocrine hormones affect the same cell that releases them, binding to receptors on the cell surface.

TABLE 23–1 Classes of Hormones

Type	Example	Synthetic path	Mode of action
Peptide	Insulin, glucagon	Proteolytic processing of prohormone	Plasma membrane receptors; second messengers
Catecholamine	Epinephrine	From tyrosine	
Eicosanoid	PGE_1	From arachidonate (20:4 fatty acid)	
Steroid	Testosterone	From cholesterol	Nuclear receptors; transcriptional regulation
Vitamin D	1,25-Dihydroxycholecalciferol	From cholesterol	
Retinoid	Retinoic acid	From vitamin A	
Thyroid	Triiodothyronine (T_3)	From Tyr in thyroglobulin	
Nitric oxide	Nitric oxide	From arginine + O_2	Cytosolic receptor (guanylyl cyclase) and second messenger (cGMP)

- Mammals are hardly unique in possessing hormonal signaling systems.
- Insects and nematode worms have highly developed systems for hormonal regulation, with fundamental mechanisms similar to those in mammals.
- Plants, too, use hormonal signals to coordinate the activities of their tissues.

- The **peptide hormones** vary in size, from 3 to more than 200 amino acid residues.

- They include the pancreatic hormones insulin, glucagon, and somatostatin; the parathyroid hormone calcitonin; and all the hormones of the hypothalamus and pituitary.

- These hormones are synthesized on ribosomes in the form of longer, precursor proteins (prohormones), then packaged into secretory vesicles and proteolytically cleaved to form the active peptides.

- In many peptide hormones the terminal residues are modified, as in TRH.

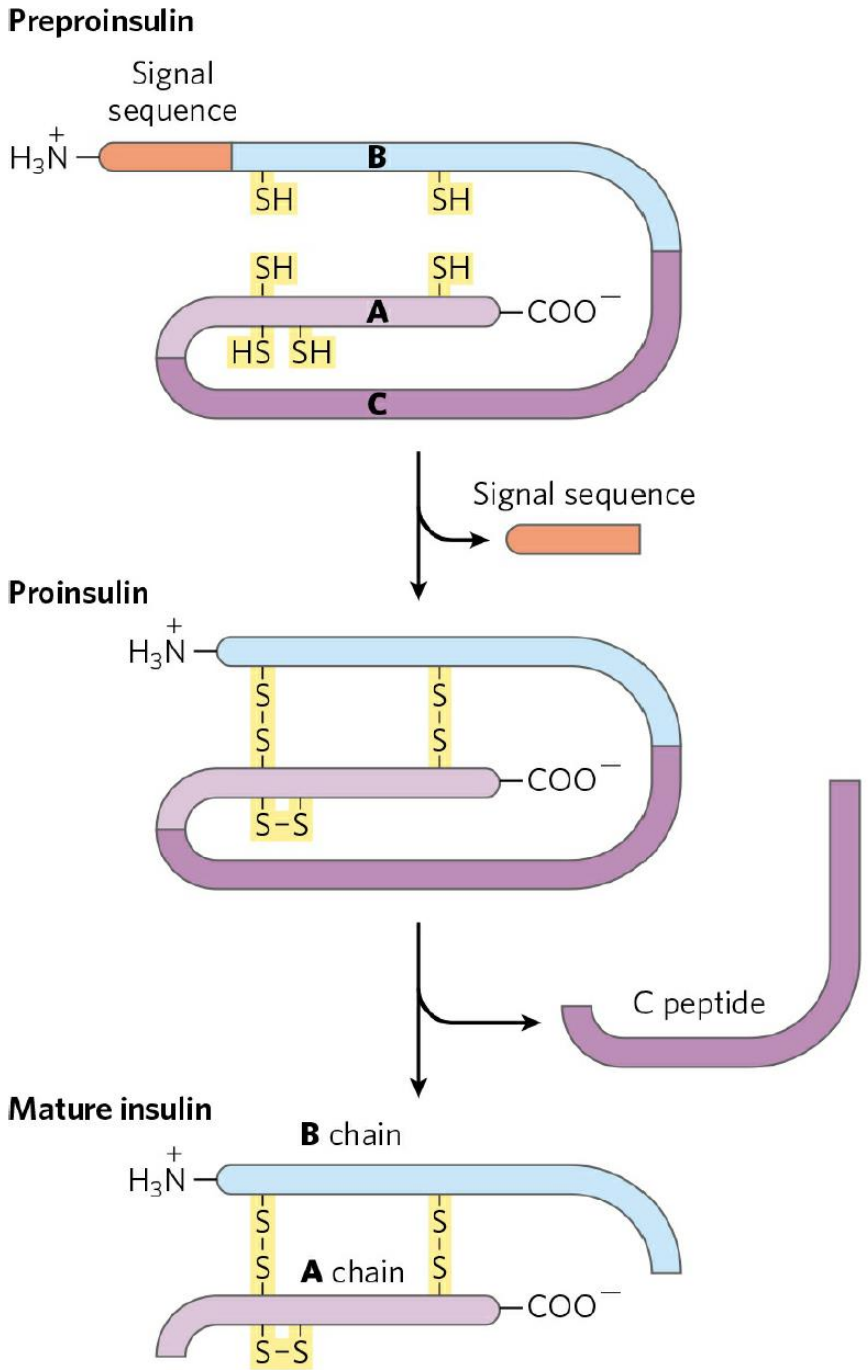
- Insulin is a small protein (Mr 5,800) with two polypeptide chains, A and B, joined by two disulfide bonds.

- It is synthesized in the pancreas as an inactive single-chain precursor, preproinsulin, with an aminoterminal “signal sequence” that directs its passage into secretory vesicles.

- Proteolytic removal of the signal sequence and formation of three disulfide bonds produces proinsulin, which is stored in secretory granules (membrane vesicles filled with protein synthesized in the ER) in pancreatic β cells.

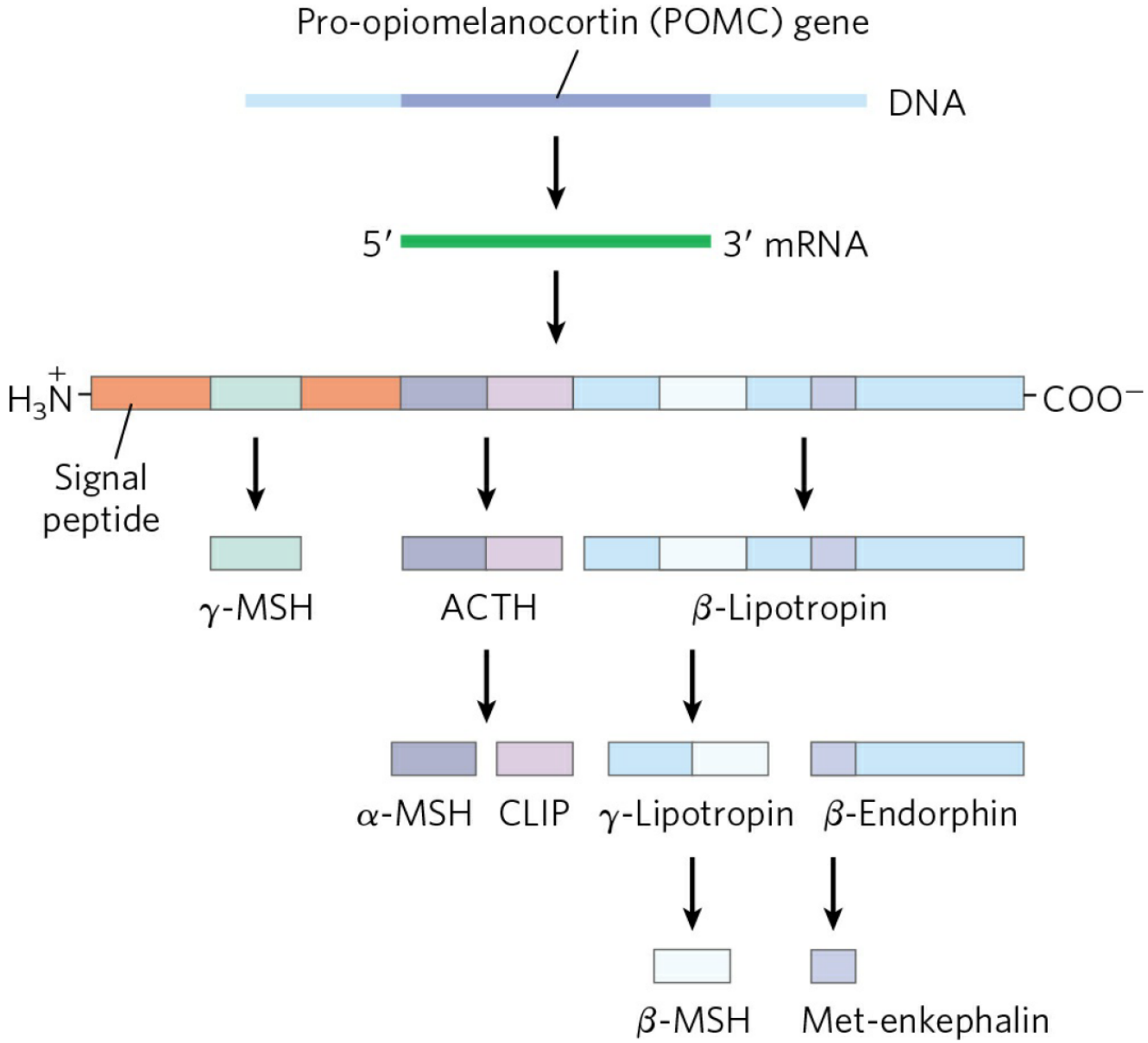
- When blood glucose is elevated sufficiently to trigger insulin secretion, proinsulin is converted to active insulin by specific proteases, which cleave two peptide bonds to form the mature insulin molecule and C peptide, which are released into the blood by exocytosis.

- All three fragments have physiological effects: insulin stimulates glucose uptake and fat synthesis, and C peptide acts through G protein–coupled receptors (GPCRs) in various tissues to mitigate effects of reduced insulin synthesis, such as diabetic nerve pain.



- There are other cases in which prohormone proteins undergo specific cleavage to produce several active hormones.

- Pro-opiomelanocortin (POMC) gene encodes a large polypeptide that is progressively carved up into at least nine biologically active peptides.



- The concentration of peptide hormones in secretory granules is so high that the vesicle contents are virtually crystalline; when the contents are released by exocytosis, a large amount of hormone is released suddenly.

- The capillaries that serve peptide-producing endocrine glands are fenestrated (punctuated with tiny holes or “windows”), so the hormone molecules readily enter the bloodstream for transport to target cells elsewhere.

- As noted earlier, all peptide hormones act by binding to receptors in the plasma membrane.

- They cause the generation of a second messenger in the cytosol, which changes the activity of an intracellular enzyme, thereby altering the cell’s metabolism.

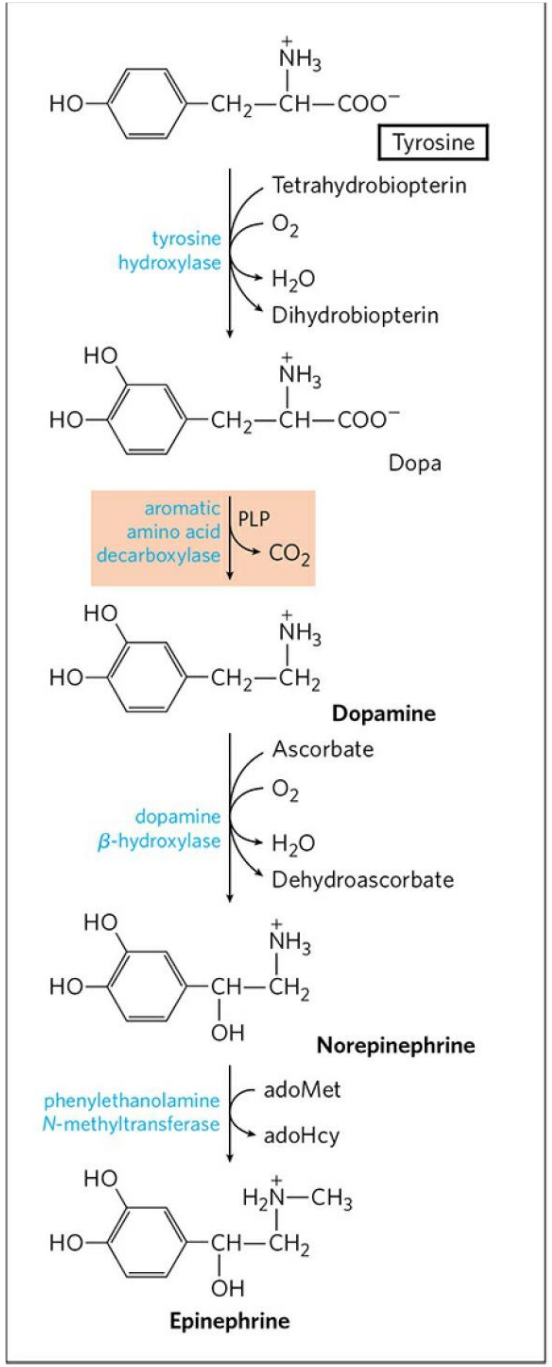
- The water-soluble compounds epinephrine (adrenaline) and norepinephrine (noradrenaline) are **catecholamines**, named for the structurally related compound catechol.

- They are synthesized from tyrosine.

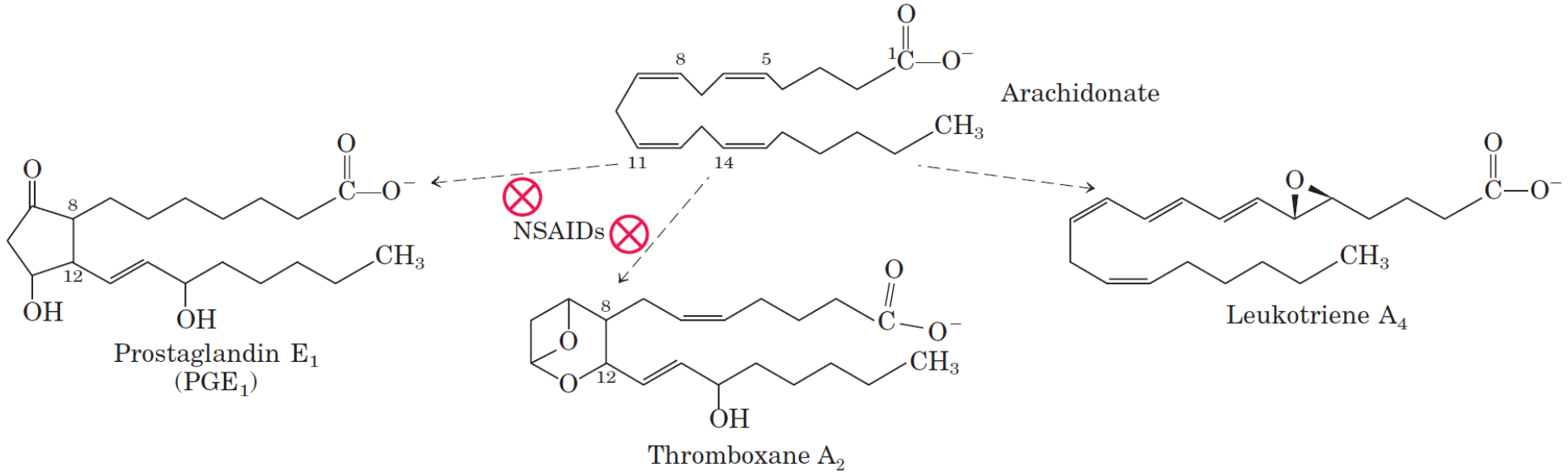
- Catecholamines produced in the brain and in other neural tissues function as neurotransmitters, but epinephrine and norepinephrine are also hormones, synthesized and secreted by the adrenal glands (adrenals).

- Like the peptide hormones, catecholamines are highly concentrated in secretory granules and released by exocytosis, and they act through surface receptors to generate intracellular second messengers.

- They mediate a wide variety of physiological responses to acute stress



❖ The **eicosanoid hormones** (prostaglandins, thromboxanes, leukotrienes, and lipoxins) are derived from the 20-carbon polyunsaturated fatty acids arachidonate (20:4($\Delta^{5,8,11,14}$) and eicosapentaenoic acid (EPA; 20:5($\Delta^{5,8,11,14,17}$).



❖ Unlike the hormones described above, they are not synthesized in advance and stored; they are produced when needed.

❖ The enzymes of the pathways leading to prostaglandins and thromboxanes are very widely distributed in mammalian tissues; most cells can produce these hormone signals, and cells of many tissues can respond to them through specific plasma membrane receptors.

- The eicosanoid hormones are paracrine hormones, secreted into the interstitial fluid (not primarily into the blood) and acting on nearby cells.

- Some prostaglandins promote the contraction of smooth muscle, including that of the intestine and uterus (and can therefore be used medically to induce labor).

- They also mediate pain and inflammation in some tissues.

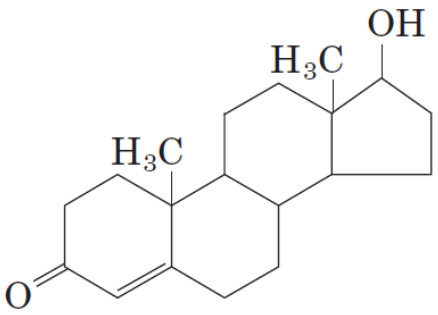
- Many antiinflammatory drugs act by inhibiting steps in prostaglandin synthetic pathways.

- Thromboxanes regulate platelet function and therefore blood clotting.

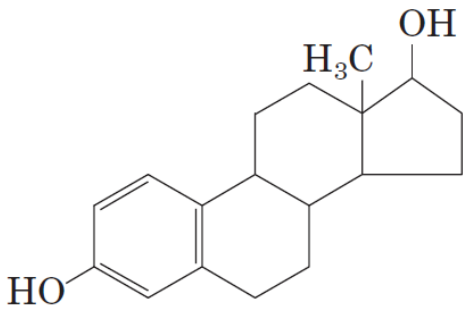
- Leukotrienes LTC4 and LTD4 act through plasma membrane receptors to stimulate contraction of smooth muscle in the intestine, pulmonary airways, and trachea.

- They are mediators of anaphylaxis, an immune overresponse that can include airway constriction, altered heartbeat, shock, and sometimes death.

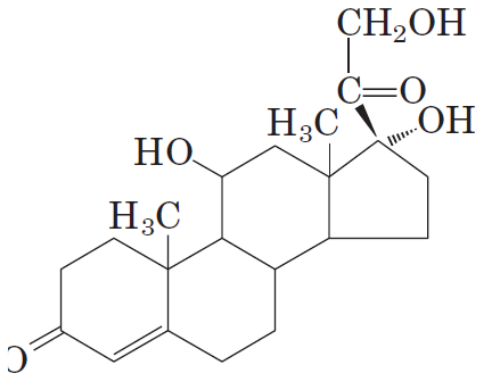
- The **steroid hormones**—corticosteroid (adrenocortical) hormones and sex hormones—are synthesized from cholesterol in several endocrine tissues.



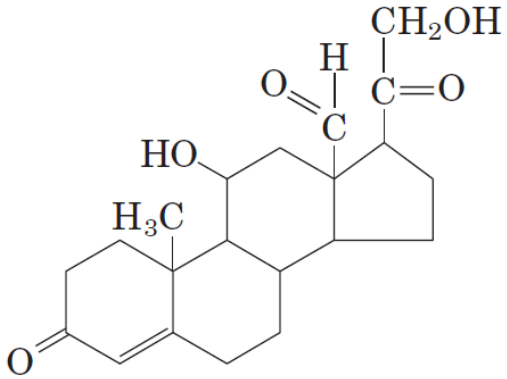
Testosterone



Estradiol



Cortisol



Aldosterone

- They travel to their target cells through the bloodstream, bound to carrier proteins.

- More than 50 corticosteroid hormones are produced in the adrenal cortex by reactions that remove the side chain from the D ring of cholesterol and introduce oxygen to form keto and hydroxyl groups.

- The corticosteroids are of two general types, defined by their actions.
- Glucocorticoids, such as cortisol, primarily affect the metabolism of carbohydrates; mineralocorticoids, such as aldosterone, regulate the concentrations of electrolytes in the blood.
- Two types of sex hormones, androgens (including testosterone) and estrogens (including estradiol), are synthesized in the testes and ovaries.
- They affect sexual development, sexual behavior, and a variety of other reproductive and nonreproductive functions.
- Their synthesis also requires cytochrome P-450 enzymes that cleave the side chain of cholesterol and introduce oxygen atoms.
- All steroid hormones act through nuclear receptors to change the level of expression of specific genes.

- They can also have more rapid effects, mediated by receptors in the plasma membrane.

- Humans and other animals are exposed to many exogenous chemicals broadly referred to as “endocrine disruptors,” ranging from environmental pollutants such as PCBs (polychlorinated biphenyls), pesticides, and pharmaceuticals to naturally occurring estrogens in plants, such as in soy products.

- Some endocrine disruptors bind to nuclear steroid receptors and stimulate hormone-like effects; others block the receptors, preventing stimulation by endogenous hormones, or interfere with the normal metabolism of steroid hormones in the liver.

- **Calcitriol** (1α,25-dihydroxycalcitriol) is produced from **vitamin D** by enzyme-catalyzed hydroxylation in the liver and kidneys.

- Vitamin D is obtained in the diet or by photolysis of 7-dehydrocholesterol in skin exposed to sunlight.

- Calcitriol works in concert with parathyroid hormone in Ca^{2+} homeostasis, regulating [Ca^{2+}] in the blood and the balance between Ca^{2+} deposition and Ca^{2+} mobilization from bone.

- Acting through nuclear receptors, calcitriol activates the synthesis of an intestinal Ca^{2+} binding protein essential for uptake of dietary Ca^{2+}.

- Inadequate dietary vitamin D or defects in the biosynthesis of calcitriol result in serious diseases such as rickets, in which bones are weak and malformed.

- The **retinoid hormones** are potent hormones that regulate the growth, survival, and differentiation of cells via nuclear retinoid receptors.

- The prohormone retinol is synthesized from β-carotene, primarily in liver, and many tissues convert retinol to the hormone retinoic acid (RA).

- RA binds its specific receptor (RAR) in the nucleus, forms a dimer with another nuclear protein, retinoid X receptor (RXR), and alters the rate of expression of genes responsive to RA.

- All tissues are retinoid targets, as all cell types have at least one form of nuclear retinoid receptor.

- In adults, the most significant targets include cornea, skin, epithelia of the lungs and trachea, and the immune system, all of which undergo constant replacement of cells.

- RA regulates the synthesis of proteins essential for growth or differentiation.

- The **thyroid hormones** T4 (thyroxine) and T3 (triiodothyronine) are synthesized from the precursor protein thyroglobulin (Mr 660,000).

- Up to 20 Tyr residues in thyroglobulin are enzymatically iodinated in the thyroid gland, then two iodotyrosine residues condense to form the precursor to thyroxine.

- When needed, thyroxine is released by proteolysis.

- Condensation of monoiodotyrosine with diiodothyronine produces T3, which is also an active hormone released by proteolysis.

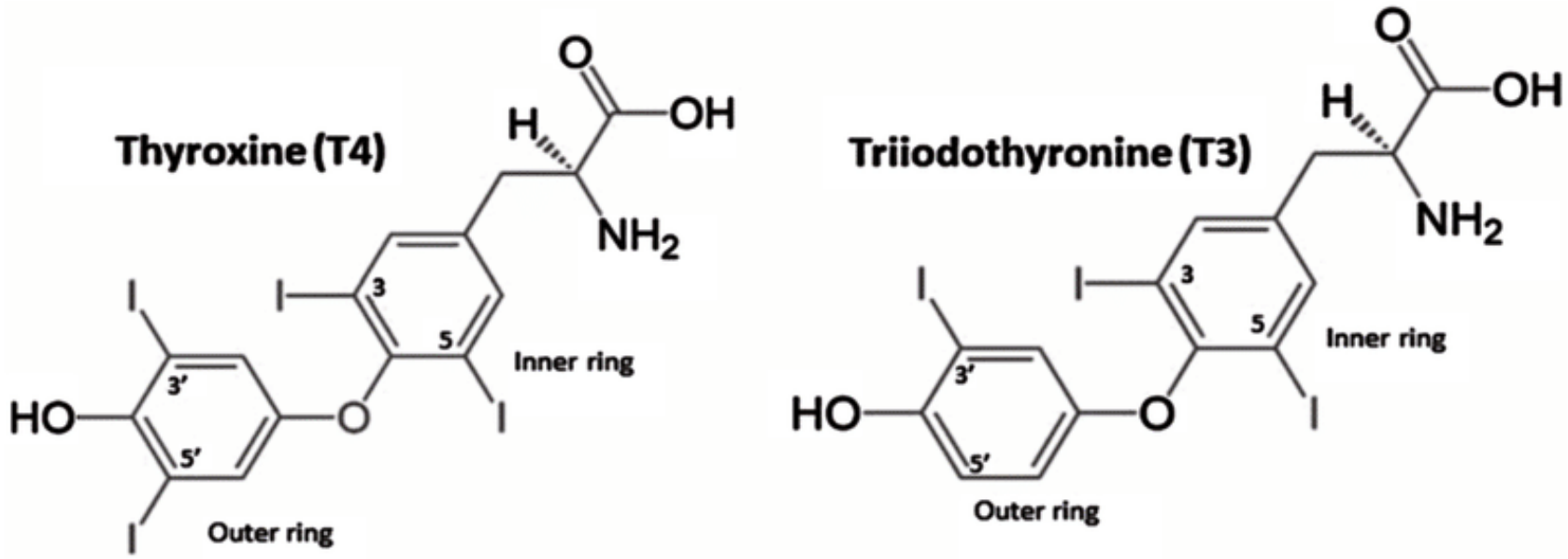
- The thyroid hormones act through nuclear receptors to stimulate energy yielding
- metabolism, especially in liver and muscle, by increasing the expression of genes encoding key catabolic enzymes.

- Underproduction of thyroxine slows metabolism and can be the cause of depression.

- When underproduction is the result of too little iodine in the diet, the thyroid gland enlarges in a futile attempt to produce more thyroxine.

- This condition, called goiter, was once common in regions far from oceans (which provide iodine in the form of fresh seafood) and areas with low-iodine soil (yielding plants with low iodine).

- Goiter has been almost eliminated in areas where iodine is routinely added to table salt.



- **Nitric oxide** is a relatively stable free radical synthesized from molecular oxygen and the guanidinium nitrogen of arginine, in a reaction catalyzed by NO synthase.

- This enzyme is found in many tissues and cell types: neurons, macrophages, hepatocytes, myocytes of smooth muscle, endothelial cells of the blood vessels, and epithelial cells of the kidney.

- NO acts near its point of release, entering the target cell and activating the cytosolic enzyme guanylyl cyclase, which catalyzes the formation of the second messenger.

- A cGMP-dependent protein kinase mediates the effects of NO by phosphorylating key proteins and altering their activities.

- For example, phosphorylation of contractile proteins in the smooth muscle surrounding blood vessels relaxes the muscle, thereby lowering blood pressure.

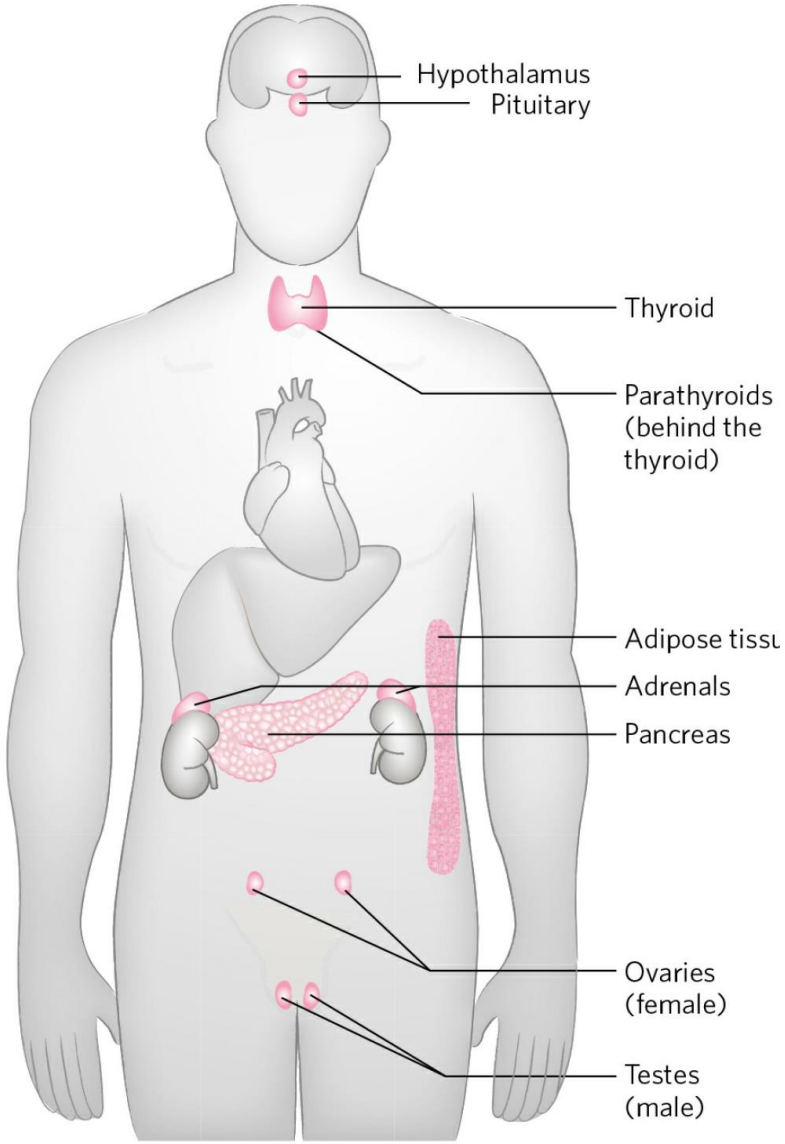
- The changing levels of specific hormones regulate specific cellular processes, but what regulates the level of each hormone?

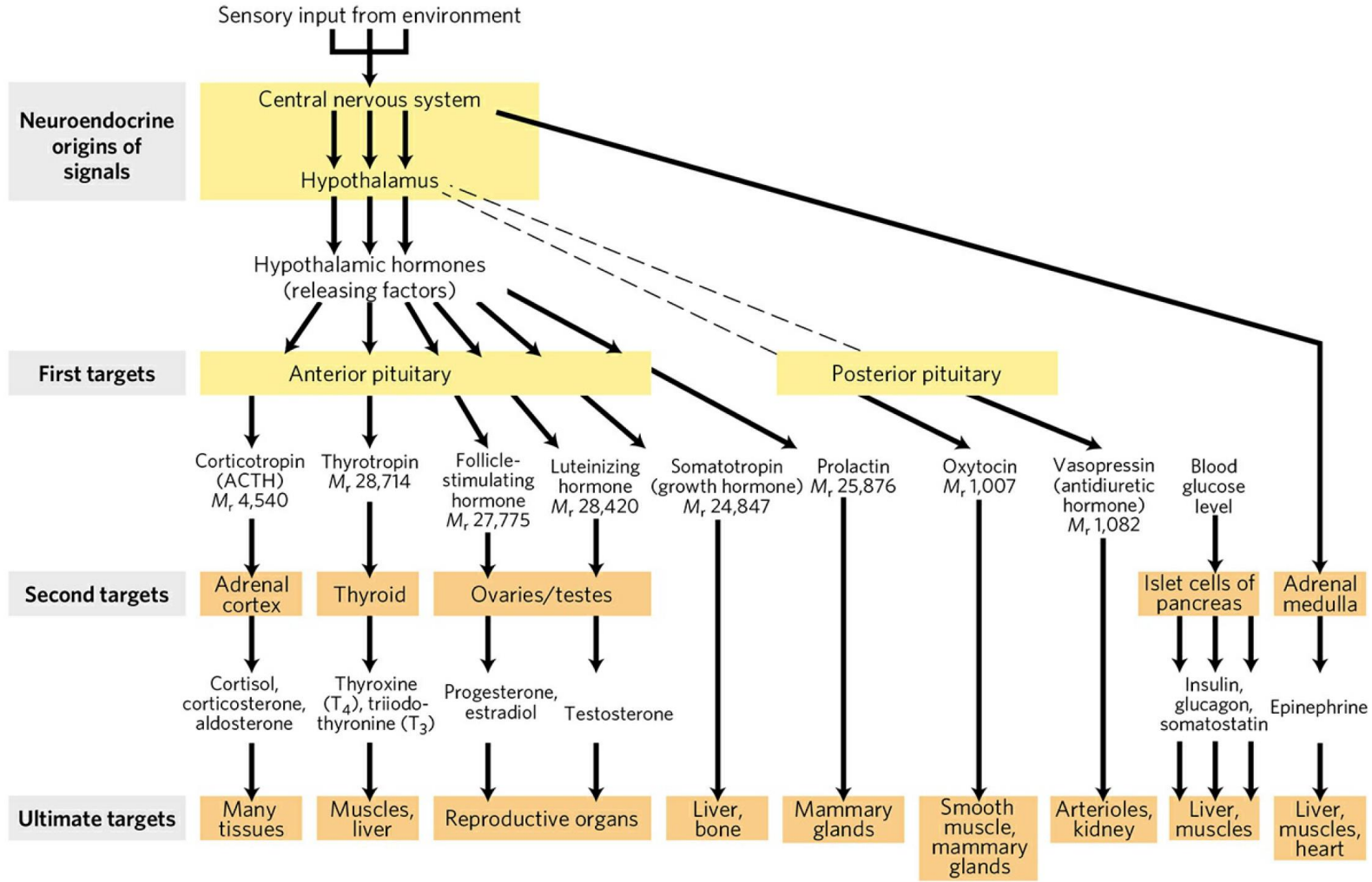
- The brief answer is that the central nervous system receives input from many internal and external sensors—signals about danger, hunger, dietary intake, blood composition and pressure, for example—and orchestrates the production of appropriate hormonal signals by the endocrine tissues.

- For a more complete answer, we must look at the hormone-producing systems of the human body and some of their functional interrelationships.

- The hypothalamus, a small region of the brain, is the coordination center of the endocrine system; it receives and integrates messages from the central nervous system.

- In response to these messages, the hypothalamus produces regulatory hormones (releasing factors) that pass directly to the nearby pituitary gland through special blood vessels and neurons that connect the two glands.


Hypothalamus
Pituitary
Thyroid
Parathyroids (behind the thyroid)
Adipose tissu
Adrenals
Pancreas
Ovaries (female)
Testes (male)


Sensory input from environment
Neuroendocrine origins of signals
Central nervous system
Hypothalamus
Hypothalamic hormones (releasing factors)
First targets
Anterior pituitary
Posterior pituitary
Corticotropin (ACTH) M_r 4,540
Thyrotropin M_r 28,714
Follicle-stimulating hormone M_r 27,775
Luteinizing hormone M_r 28,420
Somatotropin (growth hormone) M_r 24,847
Prolactin M_r 25,876
Oxytocin M_r 1,007
Vasopressin (antidiuretic hormone) M_r 1,082
Blood glucose level
Second targets
Adrenal cortex
Thyroid
Ovaries/testes
Islet cells of pancreas
Adrenal medulla
Cortisol, corticosterone, aldosterone
Thyroxine (T_4), triiodothyronine (T_3)
Progesterone, estradiol
Testosterone
Insulin, glucagon, somatostatin
Epinephrine
Ultimate targets
Many tissues
Muscles, liver
Reproductive organs
Liver, bone
Mammary glands
Smooth muscle, mammary glands
Arterioles, kidney
Liver, muscles
Liver, muscles, heart

- The pituitary gland has two functionally distinct parts.
- The posterior pituitary contains the axonal endings of many neurons that originate in the hypothalamus.
- These neurons produce the short peptide hormones oxytocin and vasopressin, which move down the axon to the nerve endings in the pituitary, where they are stored in secretory granules to await the signal for their release.
- The anterior pituitary responds to hypothalamic hormones carried in the blood, producing tropic hormones, or tropins.
- These relatively long polypeptides activate the next rank of endocrine glands, which includes the adrenal cortex, thyroid gland, ovaries, and testes.
- These glands in turn secrete their specific hormones, which are carried in the bloodstream to target tissues.

- For example, corticotropin-releasing hormone secreted from the hypothalamus stimulates the anterior pituitary to release corticotropin (ACTH), which travels through the blood to the zona fasciculata of the adrenal cortex and triggers the release of cortisol.

- Cortisol, the ultimate hormone in this cascade, acts through its receptor in many types of target cells to alter their metabolism. In hepatocytes, one effect of cortisol is to increase the rate of gluconeogenesis.

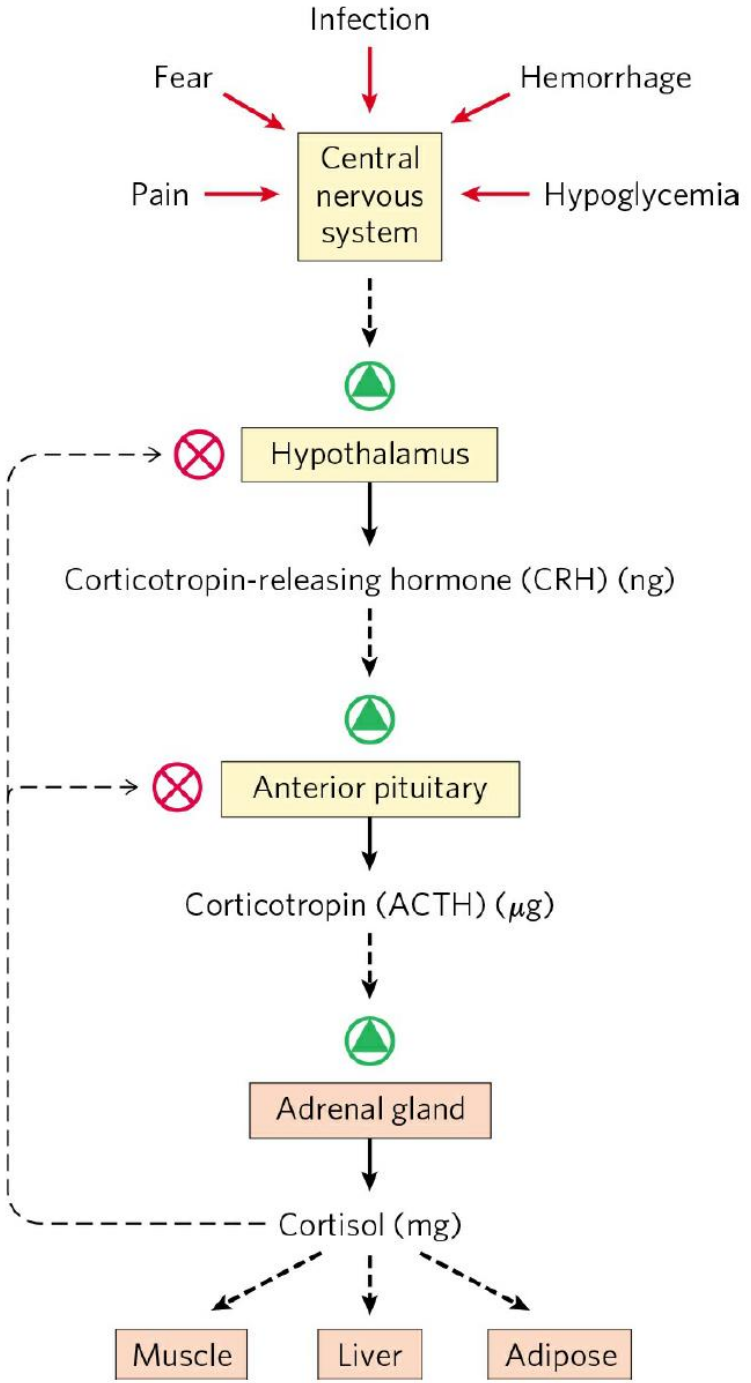
- Hormonal cascades such as those responsible for the release of cortisol and epinephrine result in large amplifications of the initial signal and allow fine-tuning of the output of the ultimate hormone.

- For example, the initial electrical signal to the hypothalamus results in the release of a few nanograms of corticotropin-releasing hormone, which elicits the release of a few micrograms of corticotropin.

- Corticotropin acts on the adrenal cortex to cause the release of milligrams of cortisol, for an overall amplification of at least a millionfold.

- At each level of a hormonal cascade, feedback inhibition of earlier steps in the cascade is possible; an unnecessarily elevated level of the ultimate hormone or of an intermediate hormone inhibits the release of earlier hormones in the cascade.

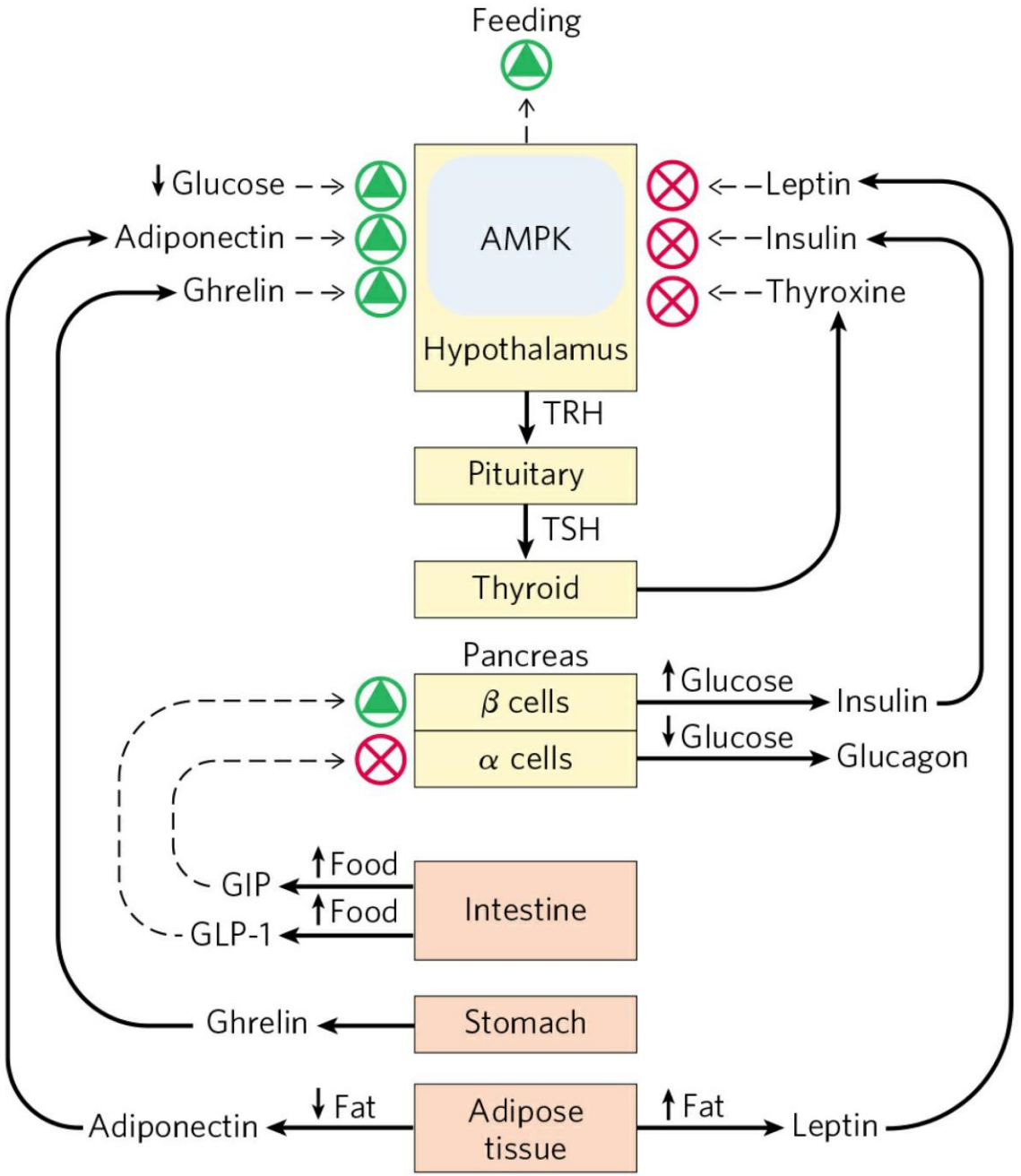
- These feedback mechanisms accomplish the same end as those that limit the output of a biosynthetic pathway: a product is synthesized (or released) only until the necessary concentration is reached.



- In addition to the top-down hierarchy of hormonal signaling, some hormones are produced in the digestive tract, muscle, and adipose tissue and communicate the current metabolic state to the hypothalamus.

- These signals are integrated in the hypothalamus, and an appropriate neuronal or hormonal response is elicited.

- The action of the enzyme AMP-activated protein kinase (AMPK) in the hypothalamus is one such integrating mechanism; it sums various inputs and passes on the information by phosphorylating key proteins in the hypothalamus.



- Adipokines, for example, are peptide hormones, produced in adipose tissue, that signal the adequacy of fat reserves.

- Leptin, released when adipose tissue is well-filled with triacylglycerols, acts in the brain to inhibit feeding behavior, whereas adiponectin signals depletion of fat reserves and stimulates feeding.

- Ghrelin is produced in the gastrointestinal tract when the stomach is empty and acts in the hypothalamus to stimulate feeding behavior; when the stomach fills, ghrelin release ceases.

- Incretins are peptide hormones produced in the gut after ingestion of a meal; they increase secretion of insulin and decrease secretion of glucagon from the pancreas.

- The best-studied of the incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), also referred to as gastric inhibitory polypeptide.

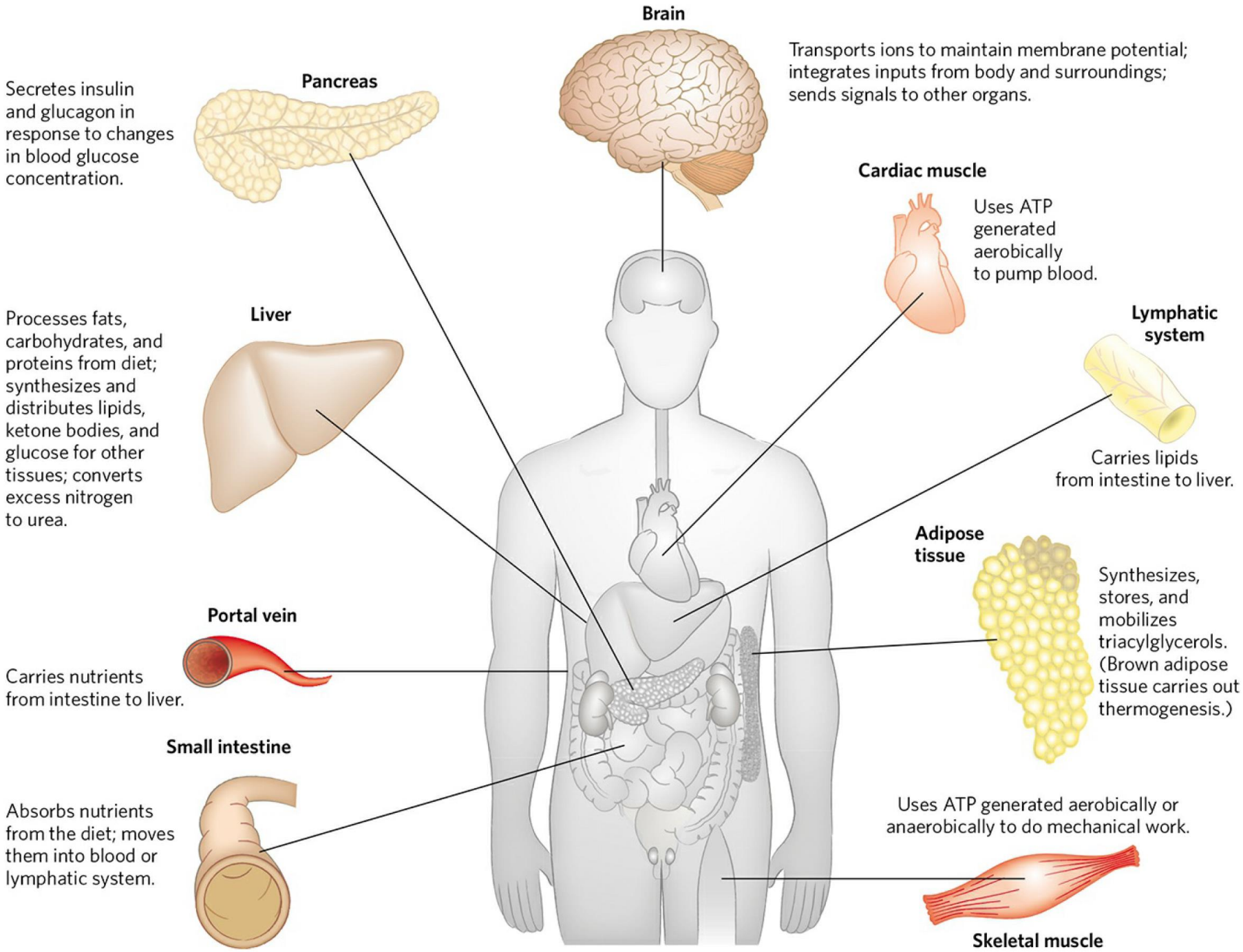
- Each tissue of the human body has a specialized function, reflected in its anatomy and metabolic activity.

- Skeletal muscle allows directed motion; adipose tissue stores and distributes energy in the form of fats, which serve as fuel throughout the body and as thermal insulation; in the brain, cells pump ions across their plasma membranes to produce electrical signals.

- The liver plays a central processing and distribution role in metabolism and furnishes all other organs and tissues with an appropriate mix of nutrients via the bloodstream.

- The functional centrality of the liver is indicated by the common reference to all other tissues and organs as “extrahepatic.”

- We begin our discussion of the division of metabolic labor by considering the transformations of carbohydrates, amino acids, and fats in the mammalian liver.


Brain
Transports ions to maintain membrane potential; integrates inputs from body and surroundings; sends signals to other organs.
Pancreas
Secretes insulin and glucagon in response to changes in blood glucose concentration.
Cardiac muscle
Uses ATP generated aerobically to pump blood.
Liver
Processes fats, carbohydrates, and proteins from diet; synthesizes and distributes lipids, ketone bodies, and glucose for other tissues; converts excess nitrogen to urea.
Lymphatic system
Carries lipids from intestine to liver.
Adipose tissue
Synthesizes, stores, and mobilizes triacylglycerols. (Brown adipose tissue carries out thermogenesis.)
Portal vein
Carries nutrients from intestine to liver.
Small intestine
Absorbs nutrients from the diet; moves them into blood or lymphatic system.
Uses ATP generated aerobically or anaerobically to do mechanical work.
Skeletal muscle

- During digestion in mammals, the three main classes of nutrients (carbohydrates, proteins, and fats) undergo enzymatic hydrolysis into their simple constituents.

- This breakdown is necessary because the epithelial cells lining the intestinal lumen absorb only relatively small molecules.

- Many of the fatty acids and monoacylglycerols released by digestion of fats in the intestine are reassembled within these epithelial cells into triacylglycerols (TAGs).

- After being absorbed, most sugars and amino acids and some reconstituted TAGs pass from intestinal epithelial cells into blood capillaries and travel in the bloodstream to the **liver**; the remaining TAGs enter adipose tissue via the lymphatic system.

- The portal vein is a direct route from the digestive organs to the liver, and the liver therefore has first access to ingested nutrients.

- The liver has two main cell types.
- Kupffer cells are phagocytes, important in immune function.
- Hepatocytes, of primary interest here, transform dietary nutrients into the fuels and precursors required by other tissues and export them via the blood.
- The kinds and amounts of nutrients supplied to the liver are determined by diet, the time between meals, and several other factors.
- The demand of extrahepatic tissues for fuels and precursors varies from one organ to another, and with the level of activity and overall nutritional state of the individual.
- To meet these changing circumstances, the liver has remarkable metabolic flexibility.
- For example, when the diet is rich in protein, hepatocytes supply themselves with high levels of enzymes for amino acid catabolism and gluconeogenesis.

- Within hours after a shift to a high carbohydrate diet, the levels of these enzymes begin to drop and the hepatocytes increase their synthesis of enzymes essential to carbohydrate metabolism and fat synthesis.

- Liver enzymes turn over (that is, are synthesized and degraded) at 5 to 10 times the rate of enzyme turnover in other tissues, such as muscle.

- Extrahepatic tissues also can adjust their metabolism to prevailing conditions, but none of these tissue are as adaptable as the liver, and none so central to the organism’s overall metabolism.

- What follows is a survey of the possible fates of sugars, amino acids, and lipids that enter the liver from the bloodstream.

- **Carbohydrates**; The glucose transporter of hepatocytes (GLUT2) allows rapid, passive diffusion of glucose, so that the concentration of glucose in a hepatocyte is essentially the same as that in the blood.

- Glucose entering hepatocytes is phosphorylated by glucokinase (hexokinase IV) to yield glucose 6-phosphate.

- Glucokinase has a much higher Km for glucose (10 mM) than do the hexokinase isozymes in other cells and, unlike these other isozymes, it is not inhibited by its product, glucose 6-phosphate.

- The presence of glucokinase allows hepatocytes to continue phosphorylating glucose when the glucose concentration rises well above levels that would overwhelm other hexokinases.

- The high Km of glucokinase also ensures that the phosphorylation of glucose in hepatocytes is minimal when the glucose concentration is low, preventing the liver from consuming glucose as fuel via glycolysis.

- This spares glucose for other tissues.

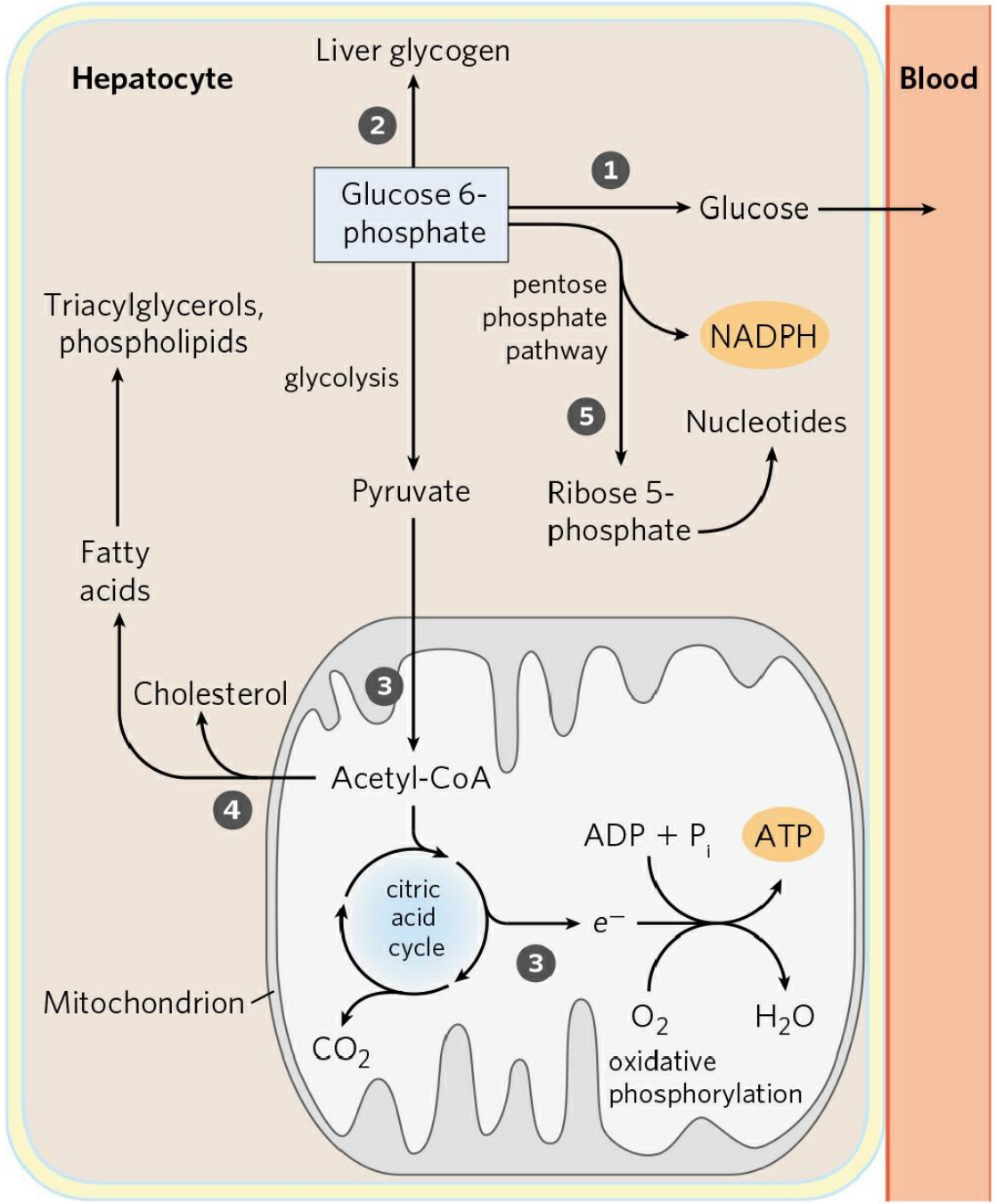
- Fructose, galactose, and mannose, all absorbed from the small intestine, are also converted to glucose 6-phosphate.

- Glucose 6- phosphate is at the crossroads of carbohydrate metabolism in the liver. It may take any of several major metabolic routes, depending on the current metabolic needs of the organism.

- By the action of various allosterically regulated enzymes, and through hormonal regulation of enzyme synthesis and activity, the liver directs the flow of glucose into one or more of these pathways.

- 1 Glucose 6-phosphate is dephosphorylated by glucose 6-phosphatase to yield free glucose, which is exported to replenish blood glucose.

- Export is the predominant pathway when glucose 6-phosphate is in limited supply, because the blood glucose concentration must be kept sufficiently high (4 to 5 mM) to provide adequate energy for the brain and other tissues.


Hepatocyte
Blood
Liver glycogen
2
Glucose 6-phosphate
1
Glucose
pentose phosphate pathway
NADPH
Triacylglycerols, phospholipids
glycolysis
5
Nucleotides
Pyruvate
Ribose 5-phosphate
Fatty acids
3
Cholesterol
Acetyl-CoA
4
ADP + P_i
ATP
citric acid cycle
e^-
3
Mitochondrion
O_2
H_2O
CO_2
oxidative phosphorylation

- 2 Glucose 6-phosphate not immediately needed to form blood glucose is converted to liver glycogen, or has one of several other fates.

- Following glycolysis and the pyruvate dehydrogenase reaction, 3 the acetyl-CoA so formed can be oxidized for ATP production by the citric acid cycle, with ensuing electron transfer and oxidative phosphorylation yielding ATP.

- (Normally, however, fatty acids are the preferred fuel for ATP production in hepatocytes.)

- 4 Acetyl-CoA can also serve as the precursor of fatty acids, which are incorporated into TAGs and phospholipids, and of cholesterol.

- Much of the lipid synthesized in the liver is transported to other tissues by blood lipoproteins.

- 5 Alternatively, glucose 6-phosphate can enter the pentose phosphate pathway, yielding both reducing power (NADPH), needed for the biosynthesis of fatty acids and cholesterol, and D-ribose 5-phosphate, a precursor for nucleotide biosynthesis.

- NADPH is also an essential cofactor in the detoxification and elimination of many drugs and other xenobiotics metabolized in the liver.

- **Amino Acids;** Amino acids that enter the liver follow several important metabolic routes.

- 1 They are precursors for protein synthesis.

- The liver constantly renews its own proteins, which have a relatively high turnover rate (average half-life of hours to days), and is also the site of biosynthesis of most plasma proteins.

- 2 Alternatively, amino acids pass in the bloodstream to other organs to be used in the synthesis of tissue proteins.

- 3 Other amino acids are precursors in the biosynthesis of nucleotides, hormones, and other nitrogenous compounds in the liver and other tissues.

- 4a Amino acids not needed as biosynthetic precursors are transaminated or deaminated and degraded to yield pyruvate and citric acid cycle intermediates, with various fates; 4b the ammonia released is converted to the excretory product urea.

- 5 Pyruvate can be converted to glucose and glycogen via gluconeogenesis, or 6 can be converted to acetyl-CoA, which has several possible fates: 7 oxidation via the citric acid cycle and 8 oxidative phosphorylation to produce ATP, or 9 conversion to lipids for storage.

- 10 Citric acid cycle intermediates can be siphoned off into glucose synthesis by gluconeogenesis.

- The liver also metabolizes amino acids that arrive intermittently from other tissues. The blood is adequately supplied with glucose just after the digestion and absorption of dietary carbohydrate or, between meals, by the conversion of liver glycogen to blood glucose.

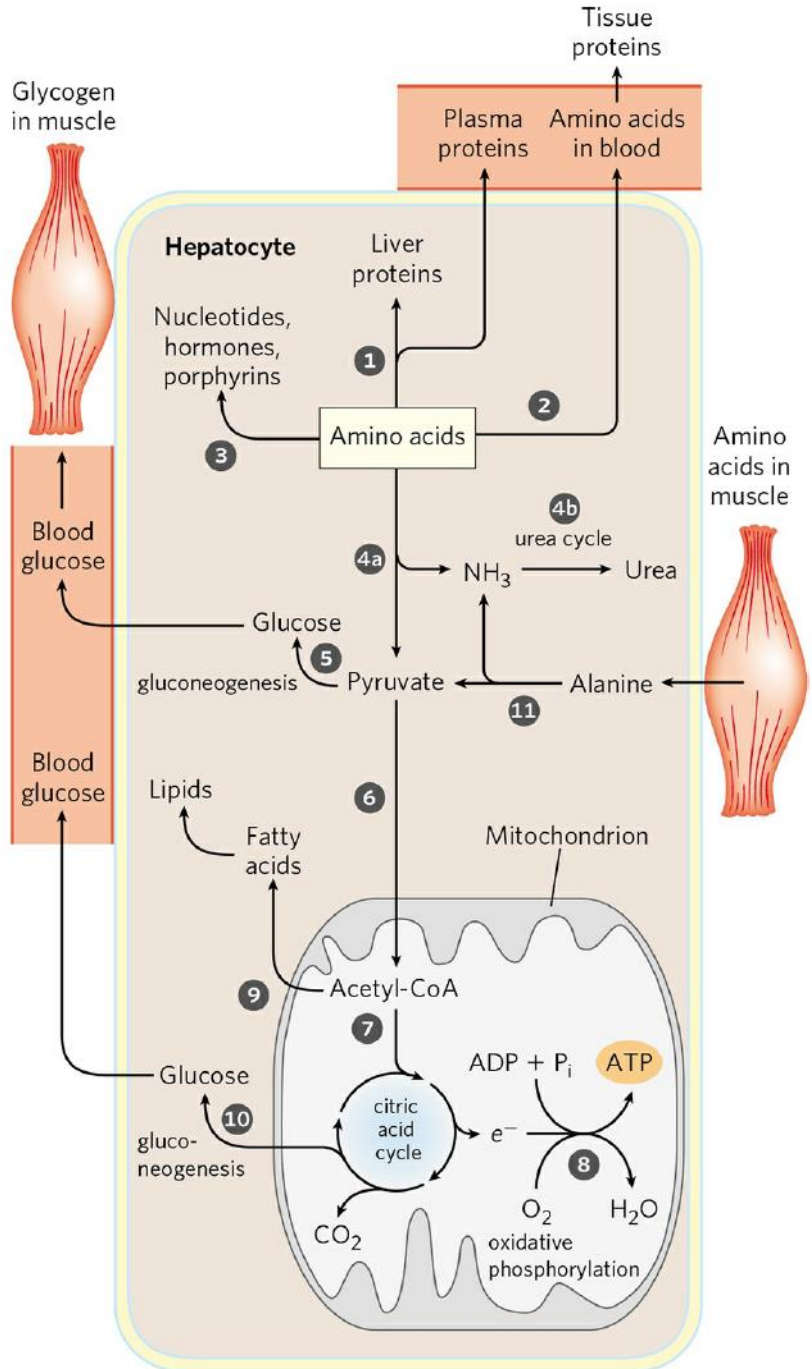
- During the interval between meals, especially if prolonged, some muscle protein is degraded to amino acids.

- These amino acids donate their amino groups (by transamination) to pyruvate, the product of glycolysis, to yield alanine, which 11 is transported to the liver and deaminated.

- Hepatocytes convert the resulting pyruvate to blood glucose via gluconeogenesis 5 , and the ammonia to urea for excretion 4b.

- One benefit of this glucose-alanine cycle is the smoothing out of fluctuations in blood glucose between meals.

- The amino acid deficit incurred in muscles is made up after the next meal by incoming dietary amino acids.


Tissue proteins
Glycogen in muscle
Plasma proteins
Amino acids in blood
Hepatocyte
Liver proteins
Nucleotides, hormones, porphyrins
1
2
3
Amino acids
Amino acids in muscle
Blood glucose
4b
urea cycle
4a
NH_3
Urea
Glucose
5
gluconeogenesis
Pyruvate
Alanine
11
Blood glucose
Lipids
6
Fatty acids
Mitochondrion
9
Acetyl-CoA
7
ADP + P_i
ATP
Glucose
10
citric acid cycle
e^-
8
gluco-neogenesis
O_2
H_2O
CO_2
oxidative phosphorylation

- **Lipids;** The fatty acid components of lipids entering hepatocytes also have several different fates.

- 1 Some are converted to liver lipids.

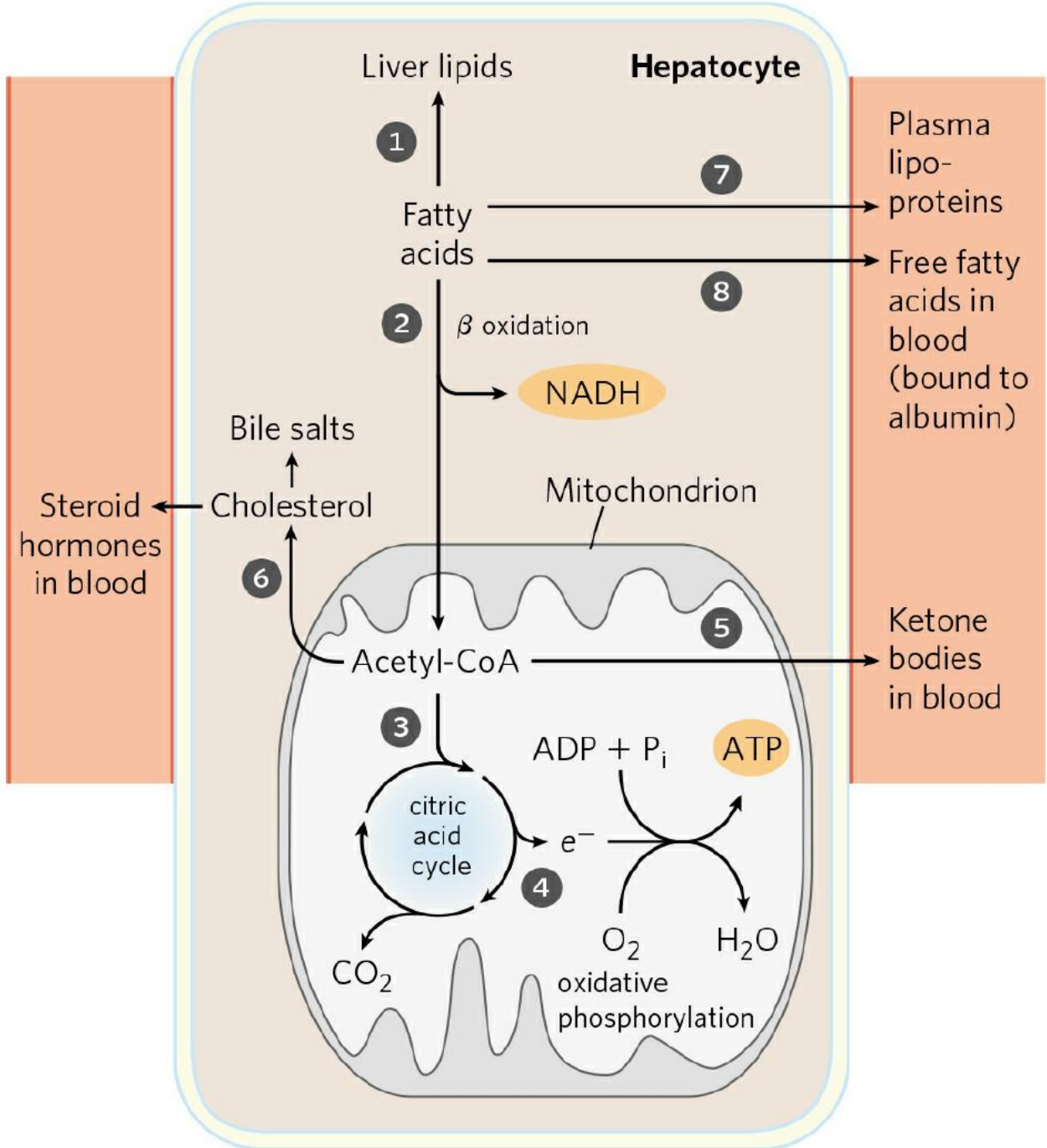
- 2 Under most circumstances, fatty acids are the primary oxidative fuel in the liver.

- Free fatty acids may be activated and oxidized to yield acetyl-CoA and NADH.

- 3 The acetyl-CoA is further oxidized via the citric acid cycle, and 4 oxidations in the cycle drive the synthesis of ATP by oxidative phosphorylation.

- 5 Excess acetyl-CoA, not required by the liver, is converted to acetoacetate and β-hydroxybutyrate; these ketone bodies circulate in the blood to other tissues to be used as fuel for the citric acid cycle.

- Ketone bodies, unlike fatty acids, can cross the blood-brain barrier, providing the brain with a source of acetyl-CoA for energy-yielding oxidation.


Liver lipids
Hepatocyte
1
Fatty acids
7
Plasma lipo-proteins
Free fatty acids in blood (bound to albumin)
8
2
β oxidation
NADH
Bile salts
Steroid hormones in blood
Cholesterol
Mitochondrion
6
5
Acetyl-CoA
Ketone bodies in blood
3
ADP + Pi
ATP
citric acid cycle
e−
4
O2
H2O
CO2
oxidative phosphorylation

- Ketone bodies can supply a significant fraction of the energy in some extrahepatic tissues—up to one-third in the heart and as much as 60% to 70% in the brain during prolonged fasting.

- 6 Some of the acetyl-CoA derived from fatty acids (and from glucose) is used for the biosynthesis of cholesterol, which is required for membrane synthesis.

- Cholesterol is also the precursor of all steroid hormones and of the bile salts, which are essential for the digestion and absorption of lipids.

- The other two metabolic fates of lipids require specialized mechanisms for the transport of insoluble lipids in blood.

- 7 Fatty acids are converted to the phospholipids and TAGs of plasma lipoproteins, which carry lipids to adipose tissue for storage.

- 8 Some free fatty acids are bound to serum albumin and carried to the heart and skeletal muscles, which take up and oxidize free fatty acids as a major fuel.

- The liver thus serves as the body's distribution center, exporting nutrients in the correct proportions to other organs, smoothing out fluctuations in metabolism caused by intermittent food intake, and processing excess amino groups into urea and other products to be disposed of by the kidneys.

- Certain nutrients are stored in the liver, including iron ions and vitamin A.

- The liver also detoxifies foreign organic compounds, such as drugs, food additives, preservatives, and other possibly harmful agents with no food value.

- Detoxification often includes the cytochrome P-450–dependent hydroxylation of relatively insoluble organic compounds, making them sufficiently soluble for further breakdown and excretion

- There are two types of **adipose tissue**, white and brown, with different roles, and we focus first on the more abundant of the two.

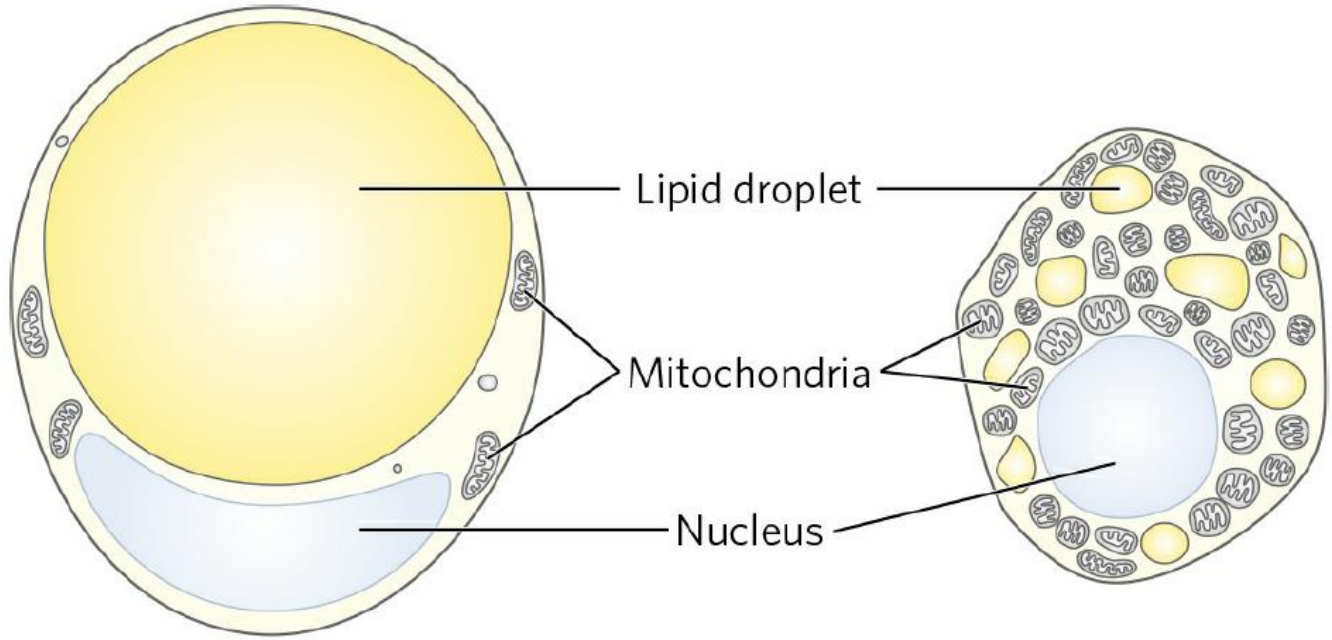
- White adipose tissue (WAT) is amorphous and widely distributed in the body: under the skin, around deep blood vessels, and in the abdominal cavity.

- The adipocytes of WAT are large (diameter 30 to 70 µm), spherical cells, completely filled with a single large lipid droplet that constitutes about 65% of the cell mass and squeezes the mitochondria and nucleus into a thin layer against the plasma membrane.

- The lipid droplet contains TAGs and sterol esters and is coated with a monolayer of phospholipids, oriented with their head groups facing the cytosol.

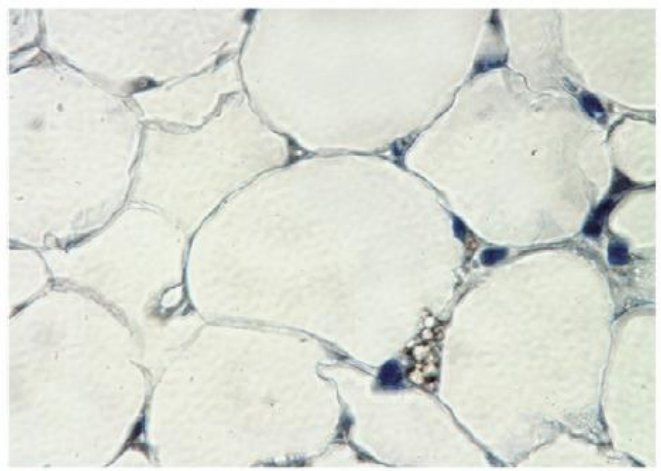
- Specific proteins are associated with the surface of the droplets, including perilipin and the enzymes for synthesis and breakdown of TAGs.

- WAT typically makes up about 15% of the mass of a healthy young adult human.

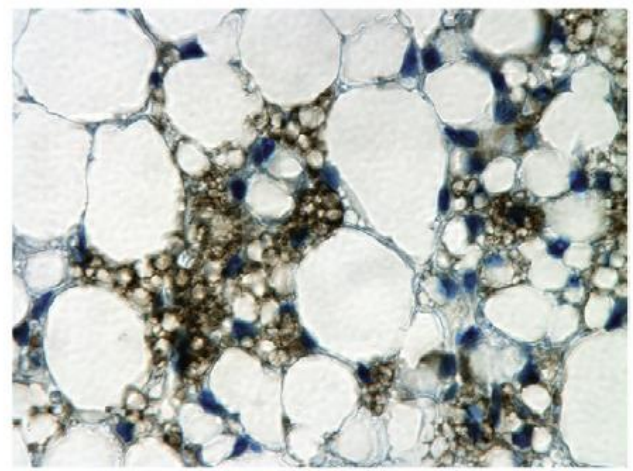


(a) White adipocyte

(b) Brown adipocyte



(c)



(d)

- Adipocytes are metabolically active, responding quickly to hormonal stimuli in a metabolic interplay with the liver, skeletal muscles, and heart.

- Like other cell types, adipocytes have an active glycolytic metabolism, oxidize pyruvate and fatty acids via the citric acid cycle, and carry out oxidative phosphorylation.

- During periods of high carbohydrate intake, adipose tissue can convert glucose (via pyruvate and acetyl-CoA) to fatty acids, convert the fatty acids to TAGs, and store the TAGs as large lipid droplets—although in humans, much of the fatty acid synthesis occurs in hepatocytes.

- Adipocytes store TAGs arriving from the liver (carried in the blood as VLDL) and from the intestinal tract (carried in chylomicrons), particularly after meals rich in fat.

- When the demand for fuel rises (between meals, for example), lipases in adipocytes hydrolyze stored TAGs to release free fatty acids, which can travel in the bloodstream to skeletal muscle and the heart.

- The release of fatty acids from adipocytes is greatly accelerated by epinephrine, which stimulates the cAMP-dependent phosphorylation of perilipin and thus gives lipases specific for tri-, di-, and monoacylglycerols access to TAGs in lipid droplets.

- Hormone-sensitive lipase is also stimulated by phosphorylation, but this is not the main cause of increased lipolysis.

- Insulin counterbalances this effect of epinephrine, decreasing the activity of the lipase.

- The breakdown and synthesis of TAGs in adipose tissue constitute a substrate cycle; up to 70% of the fatty acids released by the three lipases are reesterified in adipocytes, re-forming TAGs.

- Such substrate cycles allow fine regulation of the rate and direction of flow of intermediates through a bidirectional pathway.

- In adipose tissue, glycerol liberated by adipocyte lipases cannot be reused in the synthesis of TAGs, because adipocytes lack glycerol kinase.

- Instead, the glycerol phosphate required for TAG synthesis is made from pyruvate by glyceroneogenesis, requiring the action of the cytosolic PEP carboxykinase.

- In addition to its central function as a fuel depot, adipose tissue plays an important role as an endocrine organ, producing and releasing hormones that signal the state of energy reserves and coordinate metabolism of fats and carbohydrates throughout the body.

- In small vertebrates and hibernating animals, a significant proportion of the adipose tissue is brown adipose tissue (BAT), distinguished from WAT by its smaller, differently shaped adipocytes.

- Like white adipocytes, brown adipocytes store TAGs, but in several smaller lipid droplets per cell rather than as a single central droplet.

- BAT cells have more mitochondria and a richer supply of capillaries and innervation than WAT cells, and it is the cytochromes of mitochondria and the hemoglobin in capillaries that give BAT its characteristic brown color.

- A unique feature of brown adipocytes is their production of uncoupling protein 1 (UCP1), also called thermogenin.

- This protein is responsible for one of the principal functions of BAT: thermogenesis.

- In brown adipocytes, fatty acids stored in lipid droplets are released, enter mitochondria, and undergo complete conversion to CO_2 by β oxidation and the citric acid cycle.

- The reduced $FADH_2$ and NADH so generated pass their electrons through the respiratory chain to molecular oxygen.

- In WAT, protons pumped out of the mitochondria during electron transfer re-enter the matrix through ATP synthase, with the energy of electron transfer conserved in ATP synthesis.

- In BAT, UCP1 provides an alternative route for the reentry of protons that bypasses ATP synthase.

- The energy of the proton gradient is thus dissipated as heat, which can maintain the body (especially the nervous system and viscera) at its optimal temperature when the ambient temperature is relatively low.

- In the human fetus, differentiation of fibroblast pre-adipocytes into BAT begins at the twentieth week of gestation, and at the time of birth, BAT represents 1% to 5% of total body mass.

- The brown fat deposits are located where the heat generated by thermogenesis can ensure that vital tissues— blood vessels to the head, major abdominal blood vessels, and the viscera, including the pancreas, adrenal glands, and kidneys—are not chilled as the newborn enters a world of lower ambient temperature.

- At birth, WAT development begins and BAT begins to disappear.

- Young adult humans have much-diminished deposits of BAT, ranging from 3% of all adipose tissue in males to 7% in females, making up less than 0.1% of body mass.

- However, adults have, distributed among their WAT cells, significant numbers of adipocytes that can be converted by cold exposure or by β-adrenergic stimulation into cells very similar to brown adipocytes.

- These beige adipocytes have multiple lipid droplets, are richer in mitochondria than white adipocytes, and produce UCP1, so they function effectively as heat generators.

- Brown and beige adipocytes produce heat by oxidation of their own fatty acids, but they also take up and oxidize both fatty acids and glucose from the blood at rates out of proportion to their mass.

- In adaptation to warm or cold surroundings, and in the normal differentiation of WAT, BAT, and beige adipose tissue, the nuclear transcription factor PPARγ plays a central role.

- The peptide hormone irisin, produced in muscle by exercise, triggers the development of beige adipose tissue that continues to burn fuel long after the exercise ends.

- Metabolism in **skeletal muscle** cells—myocytes—is specialized to generate ATP as the immediate source of energy for contraction.

- Moreover, skeletal muscle is adapted to do its mechanical work intermittently, on demand.

- Sometimes skeletal muscles must work at their maximum capacity for a short time, as in a 100 m sprint; at other times more prolonged work is required, as in running a marathon or in prolonged physical labor.

- There are two general classes of muscle tissue, which differ in physiological role and fuel utilization.

- Slow-twitch muscle, also called red muscle, provides relatively low tension but is highly resistant to fatigue.

- It produces ATP by the relatively slow but steady process of oxidative phosphorylation.

- Red muscle is very rich in mitochondria and is served by dense networks of blood vessels, which bring the oxygen essential to ATP production.

- Fast-twitch muscle, or white muscle, has fewer mitochondria than red muscle and is less well supplied with blood vessels, but it can develop greater tension and do so faster.

- White muscle is quicker to fatigue because, when active, it uses ATP faster than it can replace it.

- There is a genetic component to the proportion of red and white muscle in any individual, but with training, the endurance of fast-twitch muscle can be improved.

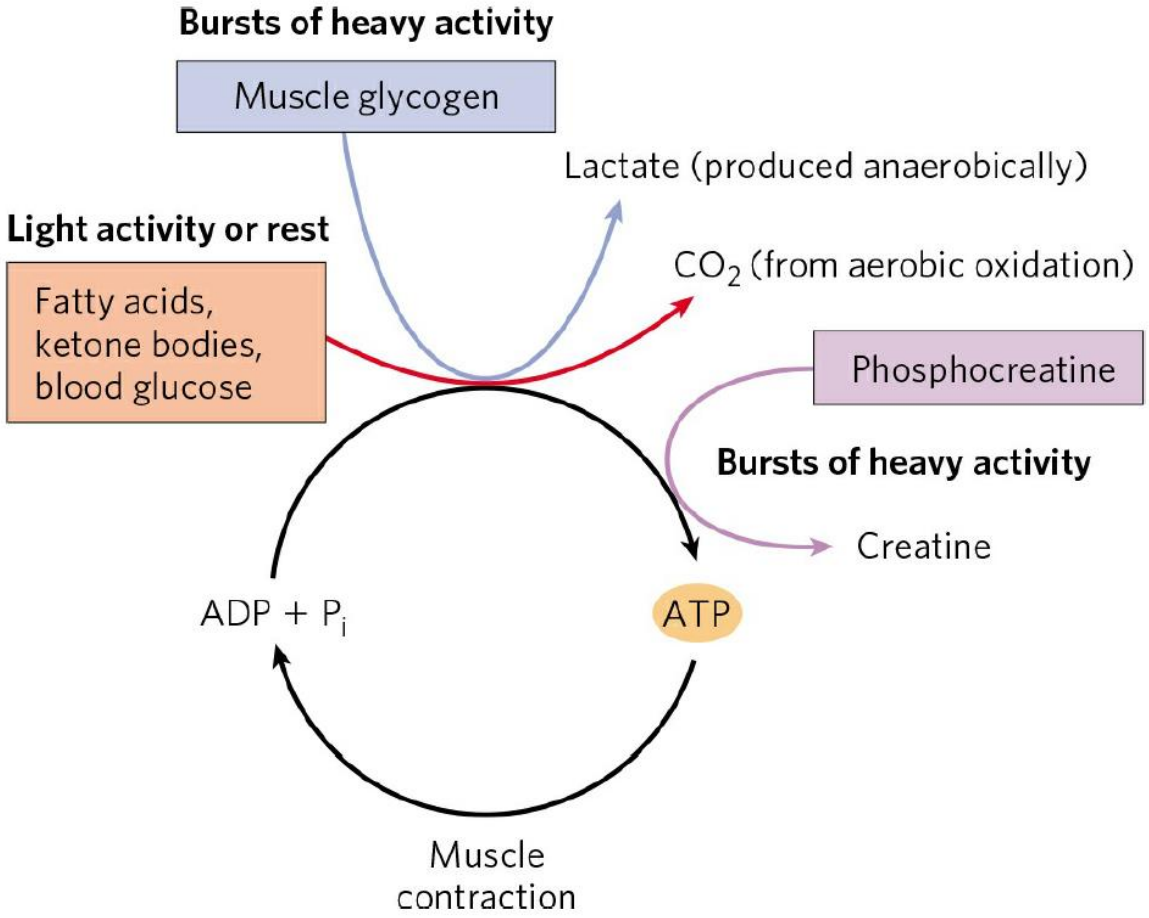
- Skeletal muscle can use free fatty acids, ketone bodies, or glucose as fuel, depending on the degree of muscular activity.

- In resting muscle, the primary fuels are free fatty acids from adipose tissue and ketone bodies from the liver.

- These are oxidized and degraded to yield acetyl-CoA, which enters the citric acid cycle, ultimately yielding the energy for ATP synthesis by oxidative phosphorylation.

- Moderately active muscle uses blood glucose in addition to fatty acids and ketone bodies.

- The glucose is phosphorylated, then degraded by glycolysis to pyruvate, which is converted to acetyl-CoA and oxidized via the citric acid cycle and oxidative phosphorylation.



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- In maximally active fast-twitch muscles, the demand for ATP is so great that the blood flow cannot provide O2 and fuels fast enough to supply sufficient ATP by aerobic respiration alone.

- Under these conditions, stored muscle glycogen is broken down to lactate by fermentation.

- Each glucose unit degraded yields three ATP, because phosphorolysis of glycogen produces glucose 6-phosphate (via glucose 1-phosphate), sparing the ATP normally consumed in the hexokinase reaction.

- Lactic acid fermentation thus responds more quickly than oxidative phosphorylation to an increased need for ATP, supplementing basal ATP production by aerobic oxidation of other fuels via the citric acid cycle and respiratory chain.

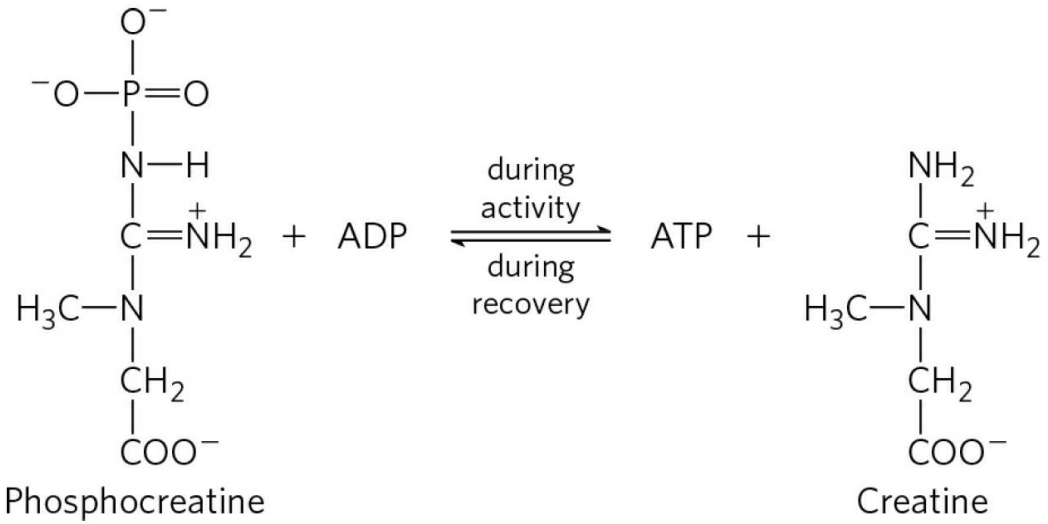
- The use of blood glucose and muscle glycogen as fuels for muscular activity is greatly enhanced by the secretion of epinephrine, which stimulates both the release of glucose from liver glycogen and the breakdown of glycogen in muscle tissue.

- Epinephrine mediates the so-called fight-or-flight response.

- The relatively small amount of glycogen (about 1% of the total weight of skeletal muscle) limits the glycolytic energy available during all-out exertion.

- Moreover, the accumulation of lactate and consequent decrease in pH in maximally active muscles reduces their efficiency.

- Skeletal muscle, however, contains another source of ATP, phosphocreatine (10 to 30 mM), which can rapidly regenerate ATP from ADP by the creatine kinase reaction.



- During periods of active contraction and glycolysis, this reaction proceeds predominantly in the direction of ATP synthesis; during recovery from exertion, the same enzyme resynthesizes phosphocreatine from creatine and ATP.

- Creatine serves to shuttle ATP equivalents from the mitochondrion to sites of ATP consumption and can be the limiting factor in the development of new muscle tissue.

- After a period of intense muscular activity, the individual continues breathing heavily for some time, using much of the extra O2 for oxidative phosphorylation in the liver.

- The ATP produced is used for gluconeogenesis (in the liver) from lactate that has been carried in the blood from the muscles.

- The glucose thus formed returns to the muscles to replenish their glycogen, completing the Cori cycle.

- Actively contracting skeletal muscle generates heat as a byproduct of imperfect coupling of the chemical energy of ATP with the mechanical work of contraction.

- This heat production can be put to good use when ambient temperature is low: skeletal muscle carries out shivering thermogenesis, rapidly repeated muscle contraction that produces heat but little motion, helping to maintain the body at its preferred temperature of 37 °C.

- **Heart muscle** differs from skeletal muscle in that it is continuously active in a regular rhythm of contraction and relaxation, and has a completely aerobic metabolism at all times.

- Mitochondria are much more abundant in heart muscle than in skeletal muscle, making up almost half the volume of the cells.

- The heart uses mainly free fatty acids as a source of energy, but also some glucose and ketone bodies taken up from the blood; these fuels are oxidized aerobically to generate ATP.

- Like skeletal muscle, heart muscle does not store lipids or glycogen in large amounts.

- It does have small amounts of reserve energy in the form of phosphocreatine, enough for a few seconds of contraction.

- Because the heart is normally aerobic and obtains its energy from oxidative phosphorylation, the failure of O2 to reach part of the heart muscle when the blood vessels are blocked by lipid deposits (atherosclerosis) or blood clots (coronary thrombosis) can cause that region of the heart muscle to die.

- This is what happens in myocardial infarction, more commonly known as a heart attack.

- The metabolism of the **brain** is remarkable in several respects.

- The neurons of the adult mammalian brain normally use only glucose as.

- Astrocytes, the other major cell type in the brain, can oxidize fatty acids.

- The brain, which constitutes about 2% of total body mass, has a very active respiratory metabolism; more than 90% of the ATP produced in the neurons comes from oxidative phosphorylation.

- The brain uses O2 at a fairly constant rate, accounting for almost 20% of the total O2 consumed by the body at rest.

- Because the brain contains very little glycogen, it is constantly dependent on incoming glucose in the blood.

- Should blood glucose fall significantly below a critical level for even a short time, severe and sometimes irreversible changes in brain function may result.

- Although the neurons of the brain cannot directly use free fatty acids or lipids from the blood as fuels, they can, when necessary, get up to 60% of their energy requirement from the oxidation of β-hydroxybutyrate (a ketone body), formed in the liver from fatty acids.

- The capacity of the brain to oxidize β-hydroxybutyrate via acetyl-CoA becomes important during prolonged fasting or starvation, after liver glycogen has been depleted, because it allows the brain to use body fat as an energy source.

- This spares muscle proteins—until they become the brain's ultimate source of glucose, via gluconeogenesis in the liver, during severe starvation.

- In neurons, energy is required to create and maintain an electrical potential across the plasma membrane.

- The membrane contains an electrogenic ATP-driven antiporter, the Na+K+ ATPase, which simultaneously pumps 2 K+ ions into and 3 Na+ ions out of the neuron.

- The resulting transmembrane potential changes transiently as an electrical signal, an action potential, sweeps from one end of a neuron to the other.

- Action potentials are the chief mechanism of information transfer in the nervous system, so depletion of ATP in neurons would have disastrous effects on all activities coordinated by neuronal signaling.

- **Blood** mediates the metabolic interactions among all tissues.

- It transports nutrients from the small intestine to the liver and from the liver and adipose tissue to other organs; it also transports waste products from extrahepatic tissues to the liver for processing and to the kidneys for excretion.

- Oxygen moves in the bloodstream from the lungs to the tissues, and CO2 generated by tissue respiration returns via the bloodstream to the lungs for exhalation.

- Blood also carries hormonal signals from one tissue to another.

- In its role as signal carrier, the circulatory system resembles the nervous system: both regulate and integrate the activities of different organs.

- The average adult human has 5 to 6 L of blood.
- Almost half of this volume is occupied by three types of blood cells:
- **erythrocytes** (red cells), filled with hemoglobin and specialized for carrying O2 and CO2;
- much smaller numbers of **leukocytes** (white cells) of several types (including lymphocytes, also found in lymphatic tissue), which are central to the immune system to defend against infections;
- and **platelets** (cell fragments), which help to mediate blood clotting.
- The liquid portion is the blood plasma, which is 90% water and 10% solutes.
- Dissolved or suspended in the plasma are many proteins, lipoproteins, nutrients, metabolites, waste products, inorganic ions, and hormones.

- More than 70% of the plasma solids are plasma proteins, primarily immunoglobulins (circulating antibodies), serum albumin, apolipoproteins (for lipid transport), transferrin (for iron transport), and blood-clotting proteins such as fibrinogen and prothrombin.

- The ions and low molecular weight solutes in blood plasma are not fixed components; they are in constant flux between blood and various tissues.

- Dietary uptake of the inorganic ions that are the predominant electrolytes of blood and cytosol (Na^+, K^+, and Ca^{2+}) is, in general, counterbalanced by their excretion in the urine.

- For many blood components, something near a dynamic steady state is achieved: the concentration of a component changes little, although a continuous flux occurs between the digestive tract, blood, and urine.

- The plasma levels of Na^+, K^+, and Ca^{2+} remain close to 140, 5, and 2.5 mM, respectively, with little change in response to dietary intake.

- Any significant departure from these values can result in serious illness or death.

- The kidneys play an especially important role in maintaining ion balance by selectively filtering waste products and excess ions out of the blood while preventing the loss of essential nutrients and ions.

- The human erythrocyte loses its nucleus and mitochondria during differentiation. It therefore relies on glycolysis alone for its supply of ATP.

- The lactate produced by glycolysis returns to the liver, where gluconeogenesis converts it to glucose, to be stored as glycogen or recirculated to peripheral tissues.

- The erythrocyte has constant access to glucose in the bloodstream.

- The minute-by-minute adjustments that keep the blood glucose level near 4.5 mM involve the combined actions of insulin, glucagon, epinephrine, and cortisol on metabolic processes in many body tissues, but especially in liver, muscle, and adipose tissue.

- Insulin signals these tissues that blood glucose is higher than necessary; as a result, cells take up excess glucose from the blood and convert it to glycogen and triacylglycerols for storage.

- Glucagon signals that blood glucose is too low, and tissues respond by producing glucose through glycogen breakdown and (in the liver) gluconeogenesis and by oxidizing fats to reduce the need for glucose.

- Epinephrine is released into the blood to prepare the muscles, lungs, and heart for a burst of activity.

- Cortisol mediates the body's response to longer-term stresses.

- Acting through plasma membrane receptors, insulin stimulates glucose uptake by muscle and adipose tissue, where the glucose is converted to glucose 6-phosphate.

- In the liver, insulin also activates glycogen synthase and inactivates glycogen phosphorylase, so that much of the glucose 6-phosphate is channelled into glycogen.

- Insulin also stimulates the storage of excess fuel as fat in adipose tissue.

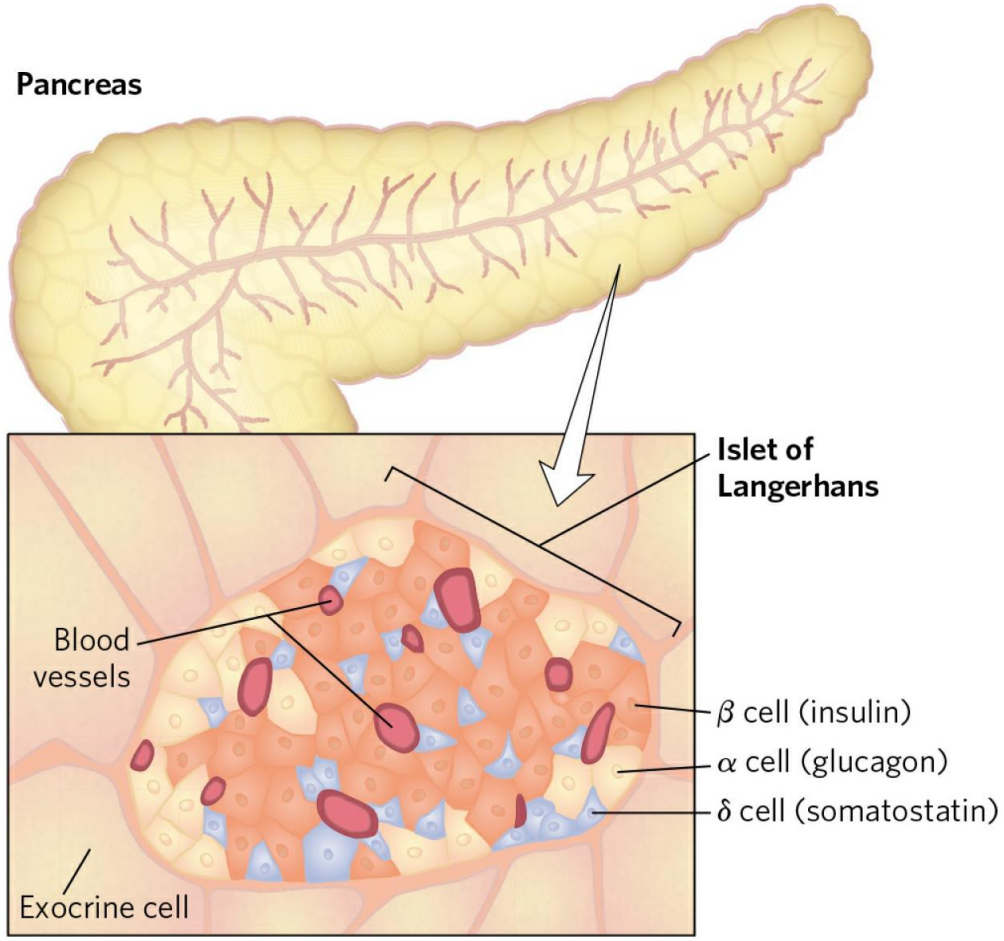
- In the liver, insulin activates both the oxidation of glucose 6-phosphate to pyruvate via glycolysis and the oxidation of pyruvate to acetyl-CoA.

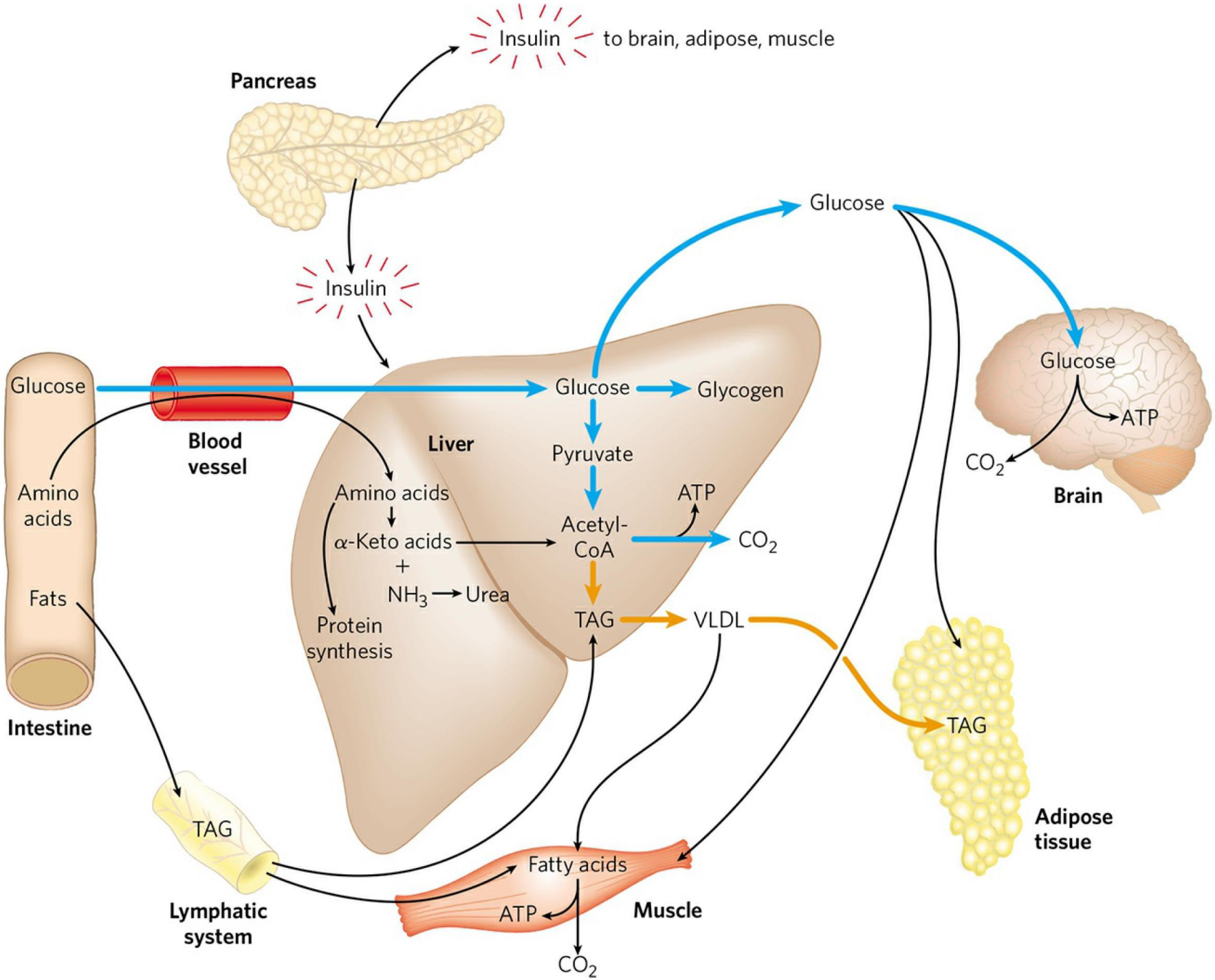
- The excess acetyl-CoA not needed for energy production is used for fatty acid synthesis, and the fatty acids are exported from the liver to adipose tissue as the TAGs of plasma lipoproteins.

- Insulin stimulates the synthesis of TAGs in adipocytes, from fatty acids released from the TAGs of VLDL.

- These fatty acids are ultimately derived from the excess glucose taken up from blood by the liver.

- In summary, the effect of insulin is to favor the conversion of excess blood glucose to two storage forms: glycogen (in the liver and muscle) and TAGs (in adipose tissue).




Insulin
to brain, adipose, muscle
Pancreas
Insulin
Glucose
Glucose
Glucose
Glycogen
Glucose
ATP
CO_2
Brain
Blood vessel
Liver
Pyruvate
Amino acids
Amino acids
ATP
Acetyl-CoA
α-Keto acids
+
NH_3 → Urea
CO_2
Fats
Protein synthesis
TAG
VLDL
Intestine
TAG
Adipose tissue
TAG
Fatty acids
ATP
Muscle
Lymphatic system
CO_2

- When glucose enters the bloodstream from the intestine after a carbohydrate-rich meal, the resulting increase in blood glucose causes increased secretion of insulin (and decreased secretion of glucagon) by the pancreas.

- Insulin release is largely regulated by the level of glucose in the blood supplying the pancreas.

- The peptide hormones insulin, glucagon, and somatostatin are produced by clusters of specialized pancreatic cells, the islets of Langerhans.

- Each cell type of the islets produces a single hormone: α cells produce glucagon; β cells, insulin; and δ cells, somatostatin.

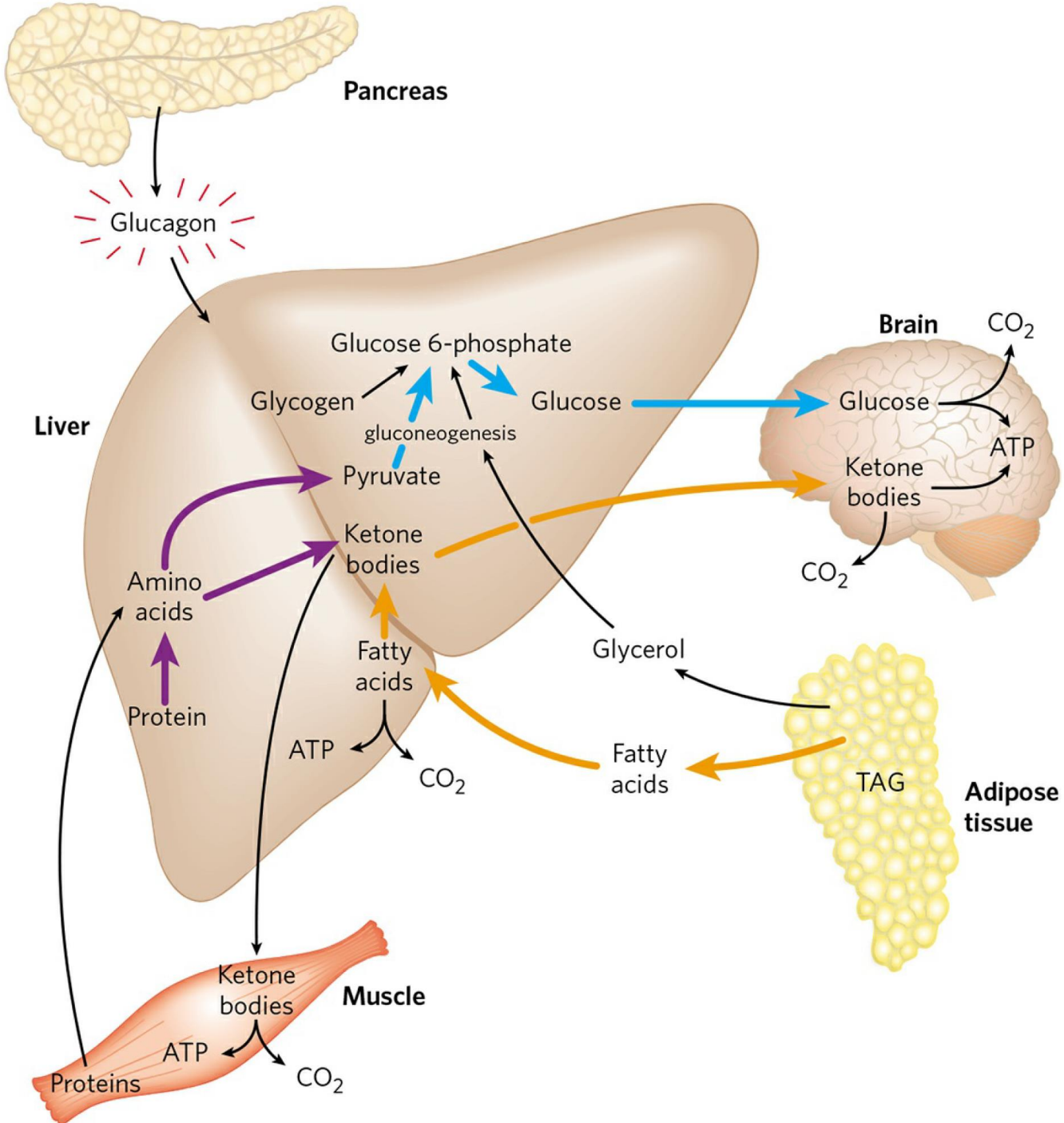
- Several hours after the intake of dietary carbohydrate, blood glucose levels fall slightly because of the ongoing oxidation of glucose by the brain and other tissues.

- Lowered blood glucose triggers secretion of glucagon and decreases insulin release.

- Glucagon causes an increase in blood glucose concentration in several ways.

- Like epinephrine, it stimulates the net breakdown of liver glycogen by activating glycogen phosphorylase and inactivating glycogen synthase; both effects are the result of phosphorylation of the regulated enzymes, triggered by cAMP.

- Glucagon inhibits glucose breakdown by glycolysis in the liver and stimulates glucose synthesis by gluconeogenesis.


Pancreas
Glucagon
Liver
Glucose 6-phosphate
Glycogen
Glucose
gluconeogenesis
Pyruvate
Ketone bodies
Amino acids
Protein
Fatty acids
ATP
CO_2
Glycerol
Brain
CO_2
Glucose
ATP
Ketone bodies
CO_2
Fatty acids
TAG
Adipose tissue
Ketone bodies
Muscle
ATP
CO_2
Proteins

- The fuel reserves of a healthy adult human are of three types: glycogen stored in the liver and, in smaller quantities, in muscles; large quantities of TAG in adipose tissues; and tissue proteins, which can be degraded when necessary to provide fuel.

- Two hours after a meal, the blood glucose level is diminished slightly, and tissues receive glucose released from liver glycogen.

- There is little or no synthesis of TAGs.

- By four hours after a meal, blood glucose has fallen further, insulin secretion has slowed, and glucagon secretion has increased.

- These hormonal signals mobilize TAGs from adipose tissue, which now become the primary fuel for muscle and liver.

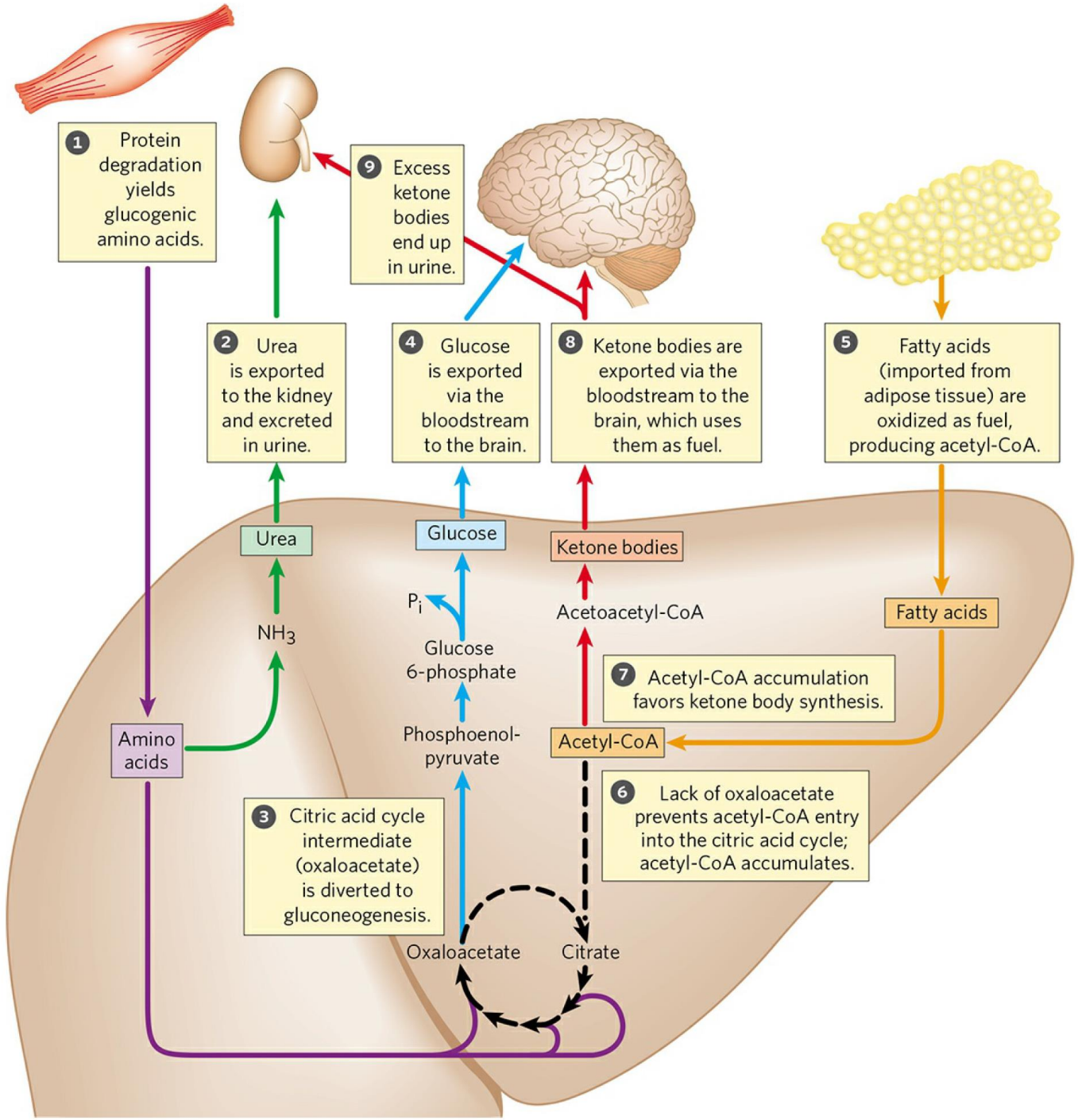

1 Protein degradation yields glucogenic amino acids.
9 Excess ketone bodies end up in urine.
2 Urea is exported to the kidney and excreted in urine.
4 Glucose is exported via the bloodstream to the brain.
8 Ketone bodies are exported via the bloodstream to the brain, which uses them as fuel.
5 Fatty acids (imported from adipose tissue) are oxidized as fuel, producing acetyl-CoA.
Urea
Glucose
Ketone bodies
Fatty acids
P_i
NH_3
Acetoacetyl-CoA
Glucose 6-phosphate
7 Acetyl-CoA accumulation favors ketone body synthesis.
Amino acids
Phosphoenol-pyruvate
Acetyl-CoA
3 Citric acid cycle intermediate (oxaloacetate) is diverted to gluconeogenesis.
6 Lack of oxaloacetate prevents acetyl-CoA entry into the citric acid cycle; acetyl-CoA accumulates.
Oxaloacetate
Citrate

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	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

*Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.

- When an animal is confronted with a stressful situation that requires increased activity—fighting or fleeing, in the extreme case—neuronal signals from the brain trigger the release of epinephrine and norepinephrine from the adrenal medulla.

- Both hormones dilate the respiratory passages to facilitate the uptake of O2, increase the rate and strength of the heartbeat, and raise the blood pressure, thereby promoting the flow of O2 and fuels to the tissues.

- This is the “fight-or-flight” response.

- Epinephrine acts primarily on muscle, adipose, and liver tissues.

- It activates glycogen phosphorylase and inactivates glycogen synthase by cAMP-dependent phosphorylation of the enzymes, thus stimulating the conversion of liver glycogen to blood glucose, the fuel for anaerobic muscular work.

- Epinephrine also promotes the anaerobic breakdown of muscle glycogen by lactic acid fermentation, stimulating glycolytic ATP formation.

- The stimulation of glycolysis is accomplished by raising the concentration of fructose 2,6-bisphosphate, a potent allosteric activator of the key glycolytic enzyme phosphofructokinase-1.

- Epinephrine also stimulates fat mobilization in adipose tissue, by activating hormone-sensitive lipase and moving aside perilipin.

- Finally, epinephrine stimulates glucagon secretion and inhibits insulin secretion, reinforcing its effect of mobilizing fuels and inhibiting fuel storage.

- A variety of stressors (anxiety, fear, pain, hemorrhage, infection, low blood glucose, starvation) stimulate release of the glucocorticoid cortisol from the adrenal cortex.

- Cortisol acts on muscle, liver, and adipose tissue to supply the organism with fuel to withstand the stress.

- Cortisol is a relatively slow-acting hormone that alters metabolism by changing the kinds and amounts of certain enzymes synthesized in its target cells, rather than by regulating the activity of existing enzyme molecules.

- In adipose tissue, cortisol leads to an increased release of fatty acids from stored TAGs.

- The exported fatty acids serve as fuel for other tissues, and the glycerol is used for gluconeogenesis in the liver.

- Cortisol stimulates the breakdown of nonessential muscle proteins and the export of amino acids to the liver, where they serve as precursors for gluconeogenesis.

- In the liver, cortisol promotes gluconeogenesis by stimulating synthesis of PEP carboxykinase; glucagon has the same effect, whereas insulin has the opposite effect.

- Glucose produced in this way is stored in the liver as glycogen or exported immediately to tissues that need glucose for fuel.

- The net effect of these metabolic changes is to restore blood glucose to its normal level and to increase glycogen stores, ready to support the fight-or-flight response commonly associated with stress.

- The effects of cortisol therefore counterbalance those of insulin.

- During extended periods of stress, the continued release of cortisol loses its positive adaptive value and begins to cause damage to muscle and bone and to impair endocrine and immune function.