References

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- اصول بیوشیمی لنینجر، ترجمه رضا محمدی، انتشارات آییژ

Metabolism: The word metabolism derives from the Greek word for “change.” Metabolism represents the sum of the chemical changes that convert nutrients, the “raw materials” necessary to nourish living organisms, into energy and the chemically complex of cells.

Is Metabolism Similar in Different Organisms?

One of the great unifying principles of modern biology is that organisms show marked similarity in their major pathways of metabolism.

TABLE 17.1 Metabolic Classification of Organisms According to Their Carbon and Energy Requirements

Classification	Carbon Source	Energy Source	Electron Donors	Examples
Photoautotrophs	CO_2	Light	H_2O, H_2S, S, other inorganic compounds	Green plants, algae, cyanobacteria, photosynthetic bacteria
Photoheterotrophs	Organic compounds	Light	Organic compounds	Nonsulfur purple bacteria
Chemoautotrophs	CO_2	Oxidation–reduction reactions	Inorganic compounds: H_2, H_2S, NH_4^+, NO_2^-, Fe^{2+}, Mn^{2+}	Nitrifying bacteria; hydrogen, sulfur, and iron bacteria
Chemoheterotrophs	Organic compounds	Oxidation–reduction reactions	Organic compounds (e.g., glucose)	All animals, most microorganisms, nonphotosynthetic plant tissue such as roots, photosynthetic cells in the dark

Metabolic classification of organisms according to use oxygen as an electron acceptor in energy-producing pathways:

Aerobes: obligate aerobes

Anaerobes: Obligate anaerobes, Facultative anaerobes

The Metabolic Map Can Be Viewed as a Set of Dots and Lines

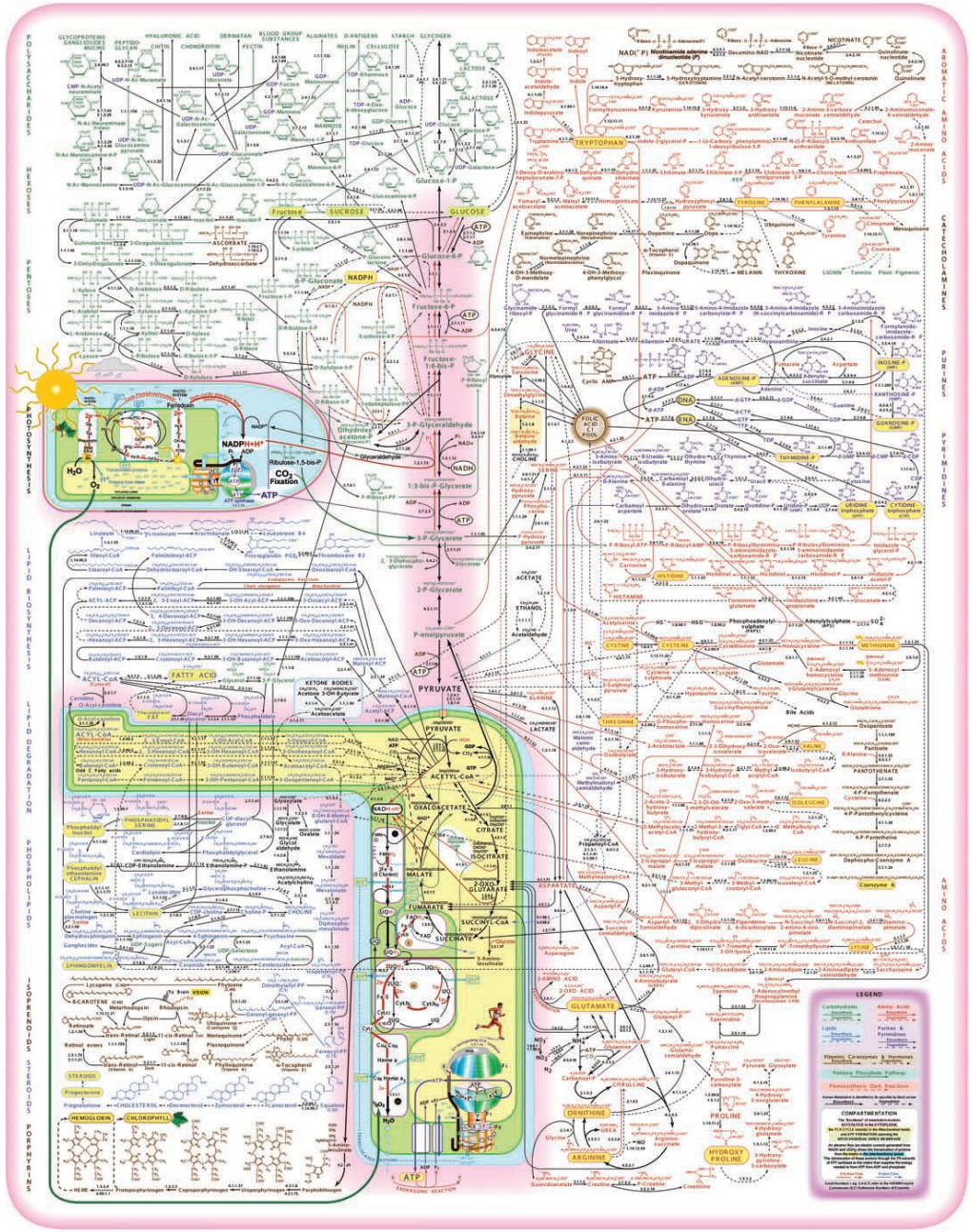


TABLE 17.2 Number of Dots (Intermediates) in the Metabolic Map of Figure 17.2, and the Number of Lines Associated with Them

Lines	Dots
1 or 2	410
3	71
4	20
5	11
6 or more	8

Figure 17.2 A metabolic map, indicating the reactions of intermediary metabolism and the enzymes that catalyze them. More than 500 different chemical intermediates, or metabolites, and a greater number of enzymes are represented here.

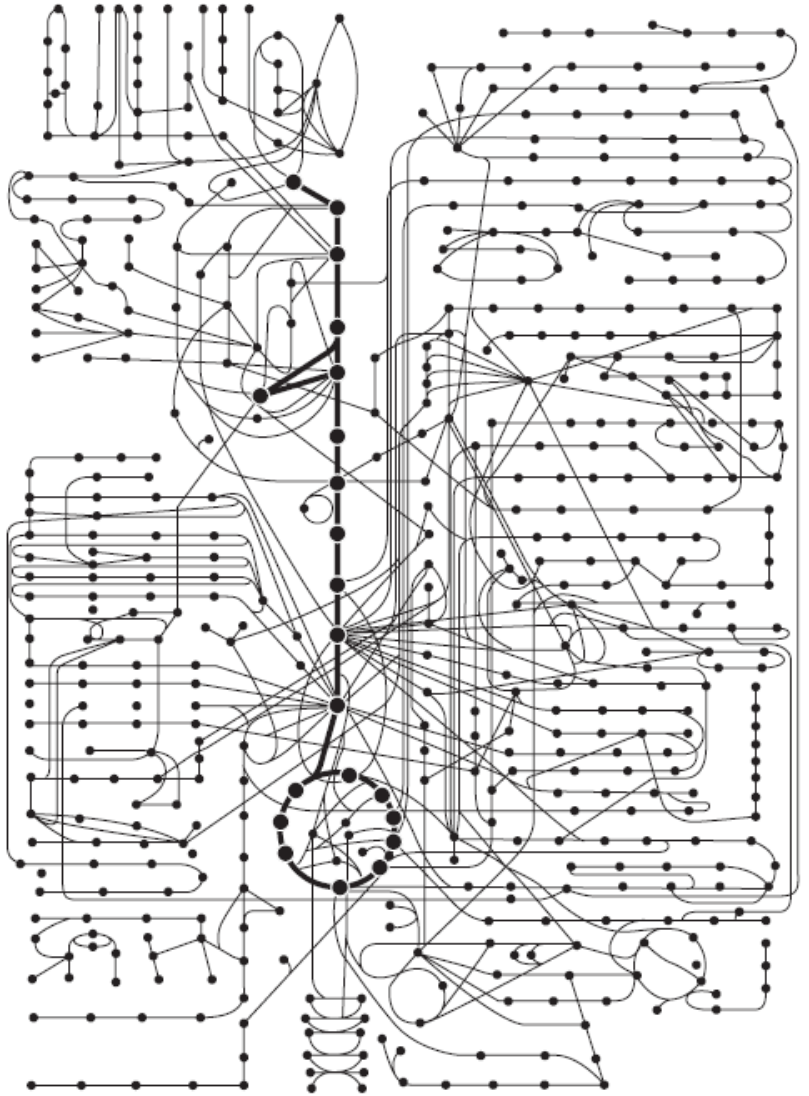


Figure 17.3 The metabolic map as a set of dots and lines. The heavy dots and lines trace the central energyreleasing pathways known as glycolysis and the citric acid cycle.

- Metabolism serves two fundamentally different purposes: the generation of energy to drive vital functions and the synthesis of biological molecules.
- To achieve these ends, metabolism consists largely of two contrasting processes: catabolism and anabolism.
- Anabolism and Catabolism Are Not Mutually Exclusive

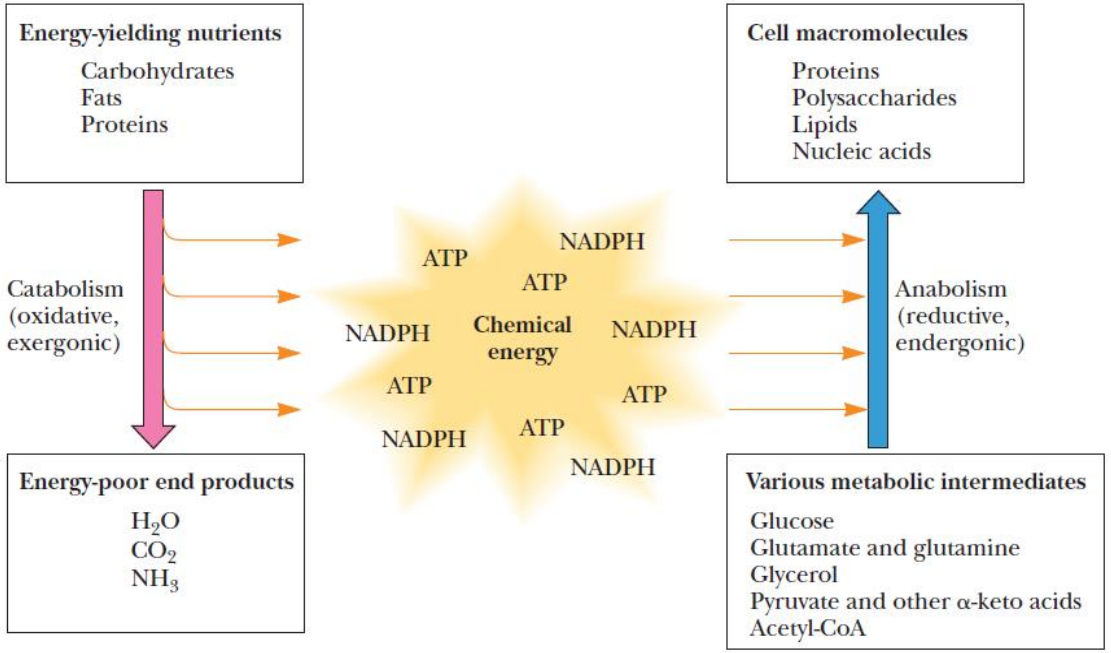


FIGURE 17.6 Energy relationships between the pathways of catabolism and anabolism. Oxidative, exergonic pathways of catabolism release free energy and reducing power that are captured in the form of ATP and NADPH, respectively. Anabolic processes are endergonic, consuming chemical energy in the form of ATP and using NADPH as a source of high-energy electrons for reductive purposes.

- Amphibolic Intermediates Play Dual Roles
- Corresponding Pathways of Catabolism and Anabolism Differ in Important Ways
- Metabolic Regulation Requires Different Pathways for Oppositely Directed Metabolic Sequences

- ATP Serves in a Cellular Energy Cycle
- NAD⁺ Collects Electrons Released in Catabolism

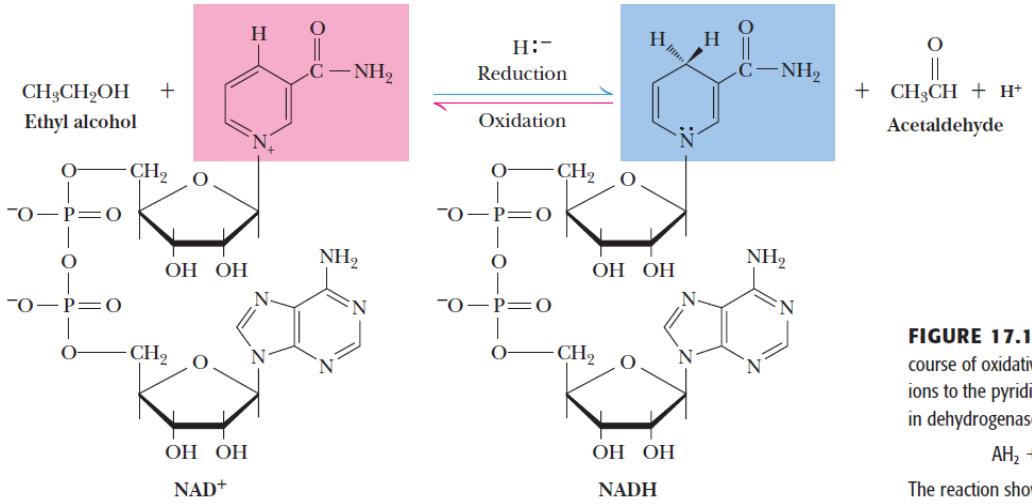


FIGURE 17.11 Hydrogen and electrons released in the course of oxidative catabolism are transferred as hydride ions to the pyridine nucleotide, NAD^+, to form NADH + H^+ in dehydrogenase reactions of the type

$$AH_2 + NAD^+ \longrightarrow A + NADH + H^+$$

The reaction shown is catalyzed by alcohol dehydrogenase.

- NADPH Provides the Reducing Power for Anabolic Processes

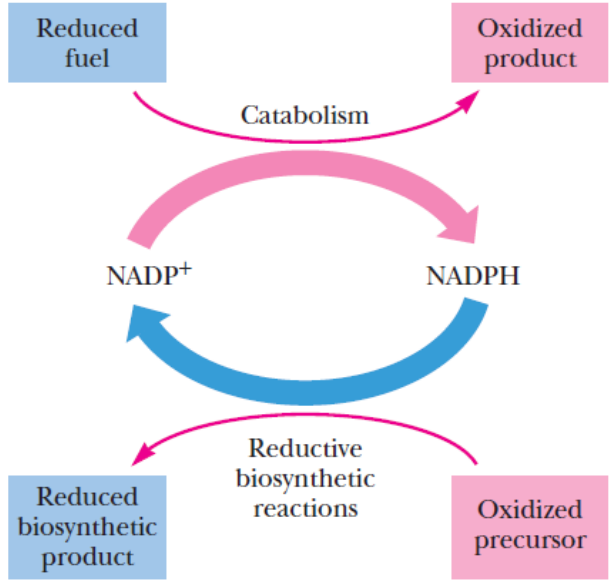


FIGURE 17.12 Transfer of reducing equivalents from catabolism to anabolism via the NADPH cycle.

- Coenzymes and Vitamins Provide Unique Chemistry and Essential Nutrients to Pathways

TABLE 17.3 Vitamins and Coenzymes

Vitamin	Coenzyme Form	Function	Discussed in Chapter
Water-Soluble			
Thiamine (vitamin B_1)	Thiamine pyrophosphate	Decarboxylation of α-keto acids and formation and cleavage of α-hydroxyketones	19, 22
Niacin (vitamin B_3, nicotinic acid)	Nicotinamide adenine dinucleotide (NAD^+)	Hydride transfer	18–27
	Nicotinamide adenine dinucleotide phosphate ($NADP^+$)	Hydride transfer	21, 22, 24–26
Riboflavin (vitamin B_2)	Flavin adenine dinucleotide (FAD)	One- and two-electron transfer	19, 20, 23, 26
	Flavin mononucleotide (FMN)	One- and two-electron transfer	20
Pantothenic acid (vitamin B_5)	Coenzyme A	Activation of acyl groups for transfer by nucleophilic attack, and activation of the α-hydrogen of the acyl group for abstraction as a proton	19, 23, 24, 27
Pyridoxal, pyridoxine, pyridoxamine (vitamin B_6)	Pyridoxal phosphate	Formation of stable Schiff base (aldimine) adducts with α-amino groups of amino acids; serving as an electron sink to stabilize reaction intermediates	25
Cobalamin (vitamin B_{12})	5′-Deoxyadenosylcobalamin	Intramolecular rearrangement, reduction of ribonucleotides to deoxyribonucleotides, and methyl group transfer	23
	Methylcobalamin		
Biotin (vitamin B_7)	Biotin–lysine complexes (biocytin)	Carrier of carboxyl groups in carboxylation reactions	22, 24
Folic acid (vitamin B_9)	Tetrahydrofolate	Acceptor and donor of 1-C units for all oxidation levels of carbon except that of CO_2	25, 26
Fat-Soluble			
Retinol (vitamin A)			
Retinal (vitamin A)			
Retinoic acid (vitamin A)			
Ergocalciferol (vitamin D_2)			
Cholecalciferol (vitamin D_3)			
α-Tocopherol (vitamin E)			
Menaquinone (vitamin K)			

Metabolism Regulation

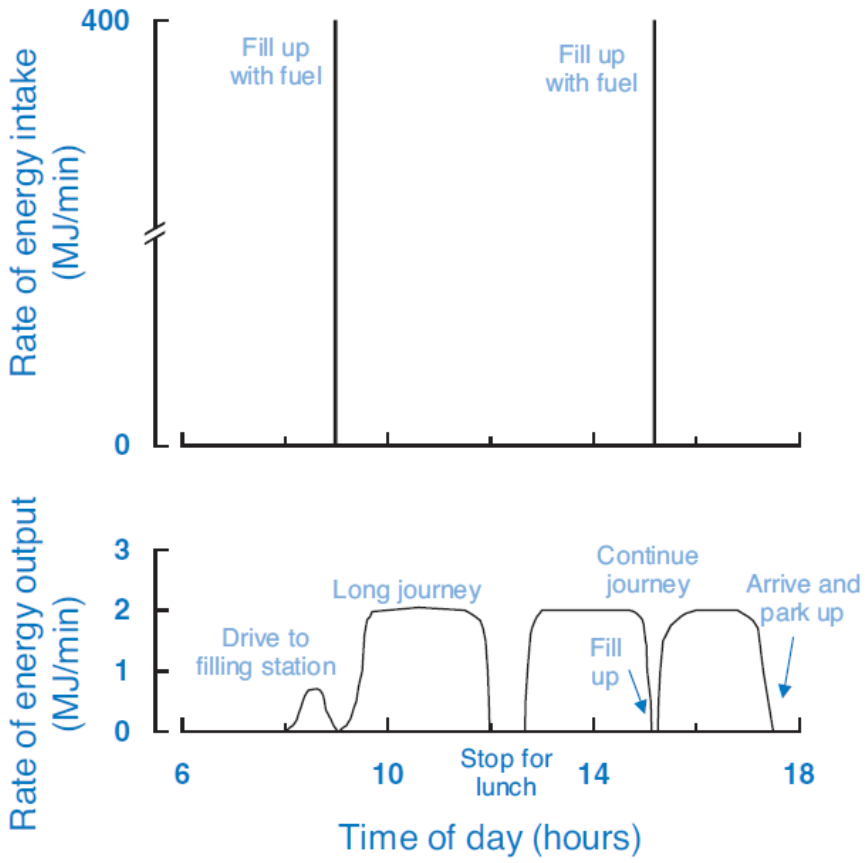


Figure 1.1 Rates of energy intake and output for a motor vehicle. The rate of intake (top panel) is zero except for periods in a filling station, when it is suddenly very high. (Notice that the scales are different for intake and output.) The rate of output is zero while the car is parked with the engine off; it increases as the car is driven to the filling station, and is relatively high during a journey. When totaled up over a long period, the areas under the two curves must be equal (energy intake = energy output) – except for any difference in the amounts of fuel in the tank before and after.

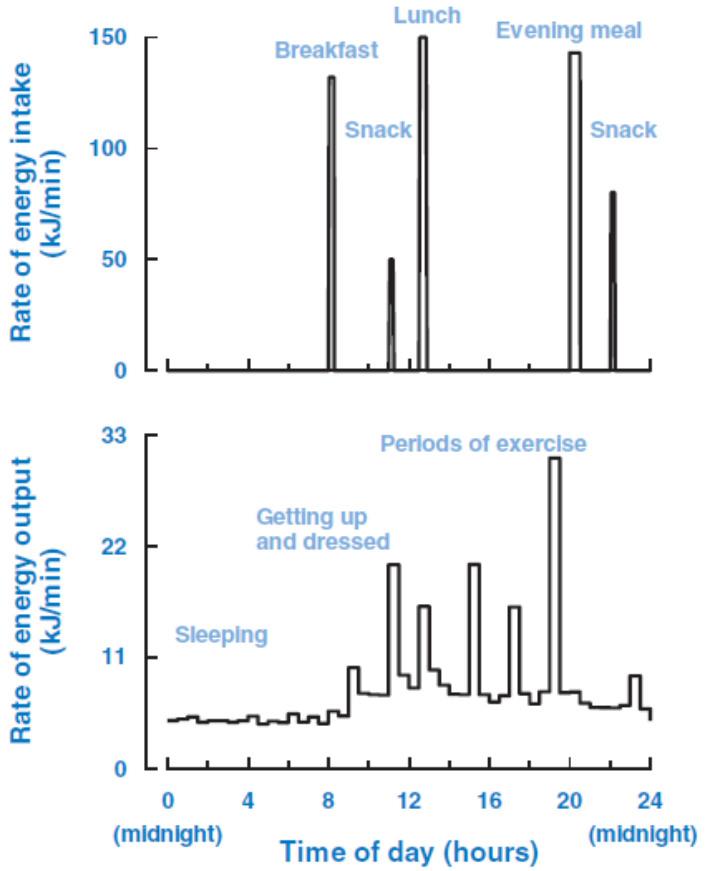


Figure 1.2 Rates of energy intake and output for a person during a typical day. The rate of energy intake (top panel) is zero except when eating or drinking, when it may be very high. The rate of energy output (heat + physical work) (lower panel) is at its lowest during sleep; it increases on waking and even more during physical activity. As with the car, the pattern of energy intake may not resemble that of energy expenditure, but over a long period the areas under the curves will balance – except for any difference in the amounts of energy stored (mainly as body fat) before and after. Data for energy expenditure are for a person measured in a calorimetry chamber and were kindly supplied by Dr Susan Jebb of MRC Human Nutrition Research, Cambridge.

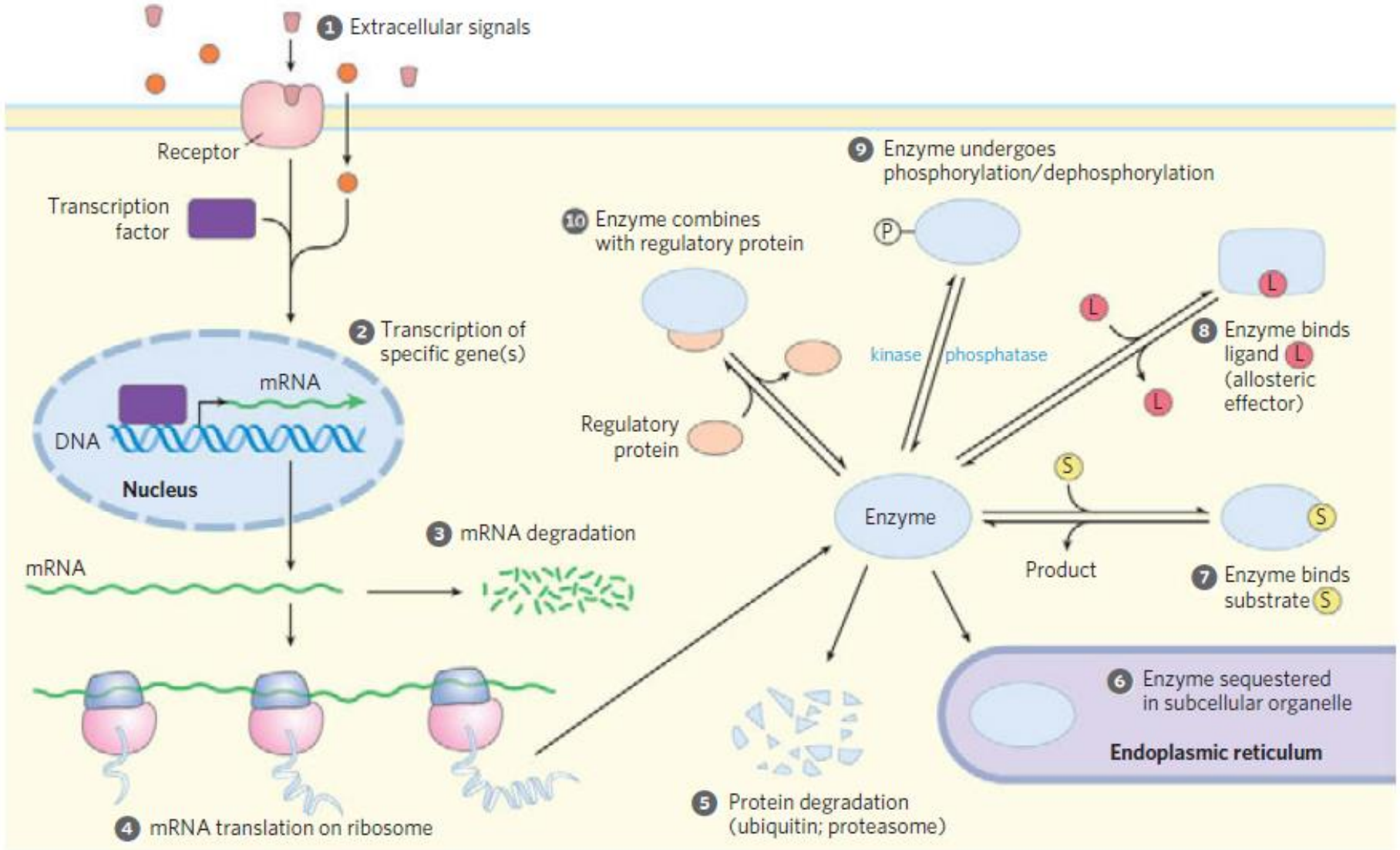
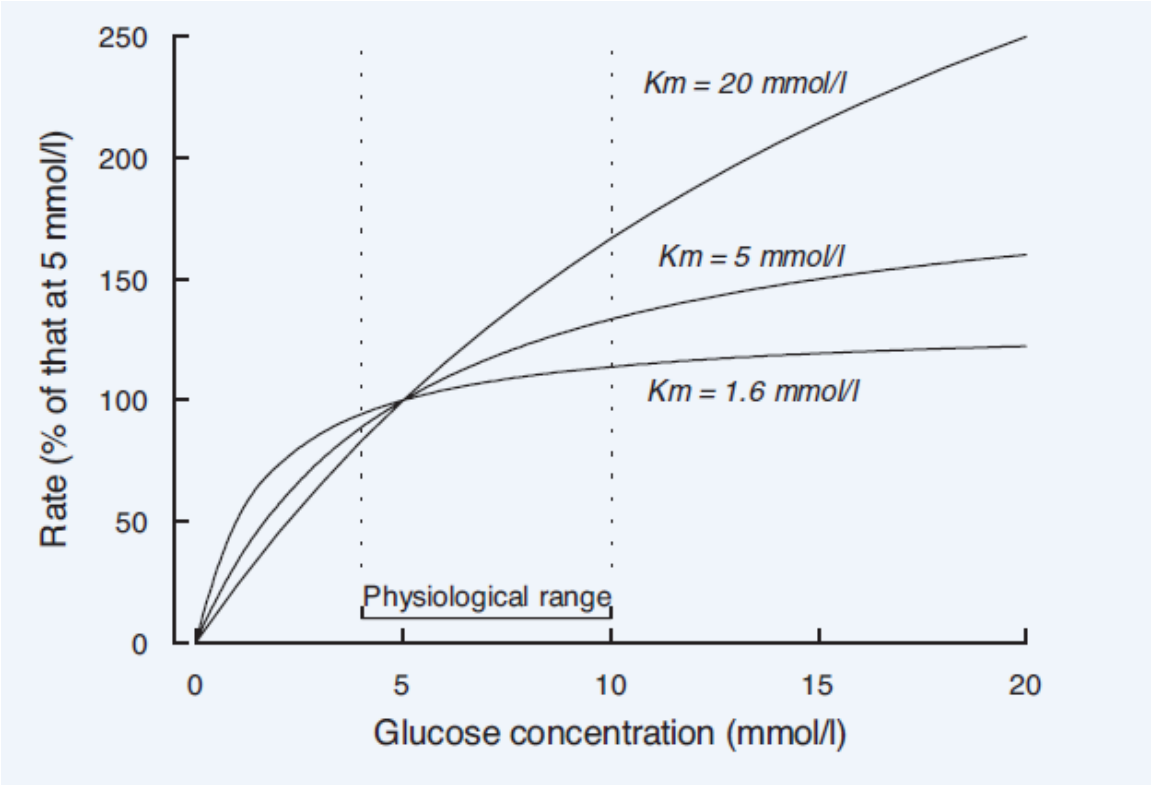


FIGURE 15–2 Factors affecting the activity of enzymes. The total activity of an enzyme can be changed by altering the *number* of its molecules in the cell, or its *effective* activity in a subcellular compartment (❶ through ❻), or by modulating the *activity* of existing molecules (❼ through ❿), as detailed in the text. An enzyme may be influenced by a combination of such factors.

Name	Tissue distribution	Approximate K_m (for inward transport of glucose or a glucose analog)	Size (no. of amino acids)	Important features
GLUT1	Erythrocytes, fetal tissue, placenta, brain blood vessels	5–7 mmol/l	492	
GLUT2	Liver, kidney, intestine, pancreatic β-cell	High (7–20 mmol/l)	524	High K_m allows glucose to "equilibrate" across the membrane
GLUT3	Brain (neuronal cells)	Low (1.6 mmol/l)	496	Low K_m allows relatively constant rate of glucose uptake independent of extracellular concentration over the normal range
GLUT4	Muscle, adipose tissue	5 mmol/l	509	The "insulin regulatable" glucose transporter: see Figure 2.3
GLUT5	Jejunum	5 mmol/l for fructose	501	Probably responsible for fructose uptake from intestine



Metabolic Regulation Brought About by the Characteristics of Tissues

The characteristics of individual cells or tissues "set the scene" for metabolic regulation. For instance, the metabolic characteristics of the liver mean that it will inevitably be able to take up excess glucose from plasma, whereas other tissues cannot adjust their rates of utilization so readily. Therefore, the liver is likely to play an important role in glucose metabolism whenever plasma glucose levels are high. The brain, in contrast, has a pathway for utilizing glucose at a rate that is relatively constant whatever the plasma glucose concentration, a very reasonable adaptation since we would not want to be super-intelligent only after eating carbohydrate, and intellectually challenged between meals.

What Experiments Can Be Used to Elucidate Metabolic Pathways?

- Mutations Create Specific Metabolic Blocks
- An important tool for elucidating the steps in the pathway was the use of metabolic inhibitors.
- Isotopic Tracers Can Be Used as Metabolic Probes
- NMR Spectroscopy Is a Noninvasive Metabolic Probe

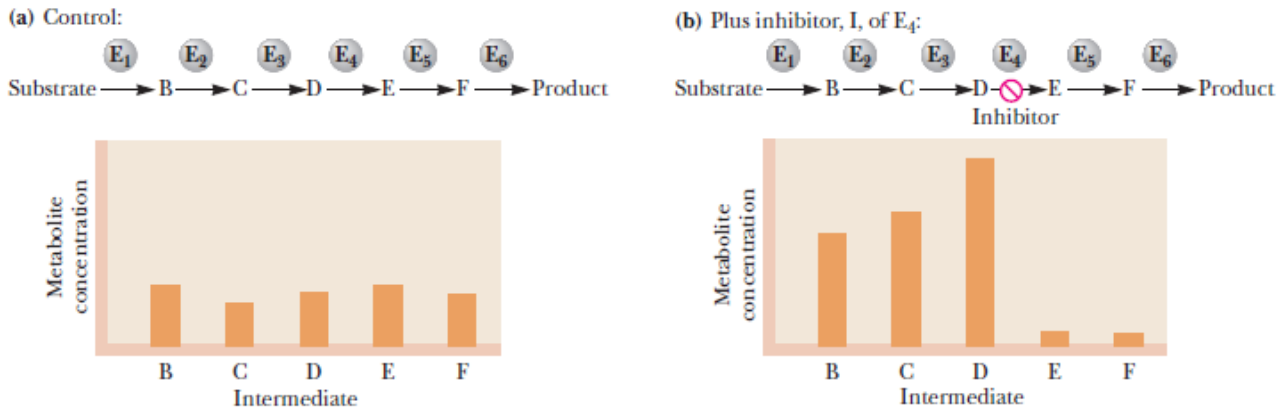


FIGURE 17.13 The use of inhibitors to reveal the sequence of reactions in a metabolic pathway. **(a) Control:** Under normal conditions, the steady-state concentrations of a series of intermediates will be determined by the relative activities of the enzymes in the pathway. **(b) Plus inhibitor:** In the presence of an inhibitor (in this case, an inhibitor of *enzyme 4*), intermediates upstream of the metabolic block (B, C, and D) accumulate, revealing themselves as intermediates in the pathway. The concentration of intermediates lying downstream (E and F) will fall.

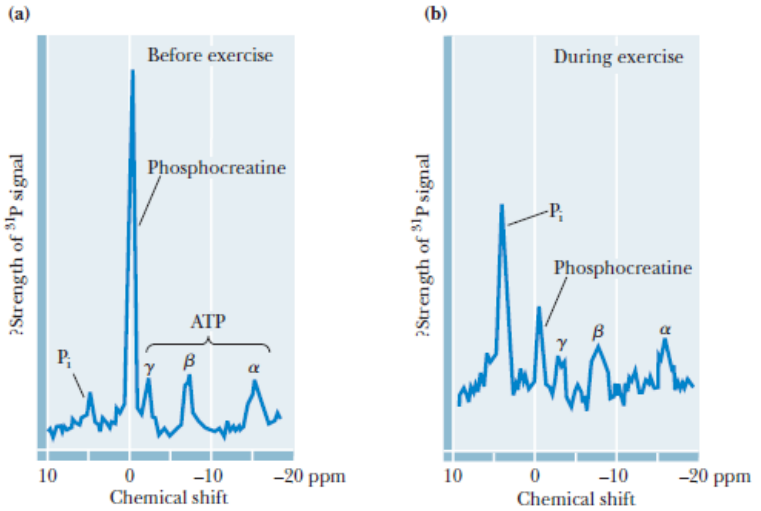


FIGURE 17.15 With NMR spectroscopy, one can observe the metabolism of a living subject in real time. These NMR spectra show the changes in ATP, creatine-P (phosphocreatine), and P_i levels in the forearm muscle of a human subjected to 19 minutes of exercise. Note that the three P atoms of ATP (α, β, and γ) have different chemical shifts, reflecting their different chemical environments.

Metabolic Pathways Are Compartmentalized Within Cells

Temporal Compartmentalization of Metabolic Pathways: Cells and organisms also exhibit temporal compartmentalization of their metabolic pathways. That is, metabolic pathways may be turned on and off in a time-dependent and/or cyclic fashion. For example, the metabolism of many organisms—microbes, animals, and plants—is regulated in synchrony with the 24-hour cycle of day and night, a pattern called circadian rhythmicity and often referred to as the biological clock. Why? Because light and/or varying nutrient availability represent key signals regarding the transitory nature of the environment, and organisms have evolved and adapted to exploit the information in such signals.

Spatial compartmentalization: In many instances, the enzymes of a metabolic sequence occur together within the organellar membrane. Thus, the flow of metabolic intermediates in the cell is spatially as well as chemically segregated. For example, the 10 enzymes of glycolysis are found in the cytosol, but pyruvate, the product of glycolysis, is fed into the mitochondria. These organelles contain the citric acid cycle enzymes, which oxidize pyruvate to CO2. The great amount of energy released in the process is captured by the oxidative phosphorylation system of mitochondrial membranes and used to drive the formation of ATP

temporal: Relating to time as distinguished from space; chronological

- ❑ Metabolomics
- ❑ Metabolome
- ❑ Fluxomics
- ❑ Fluxome

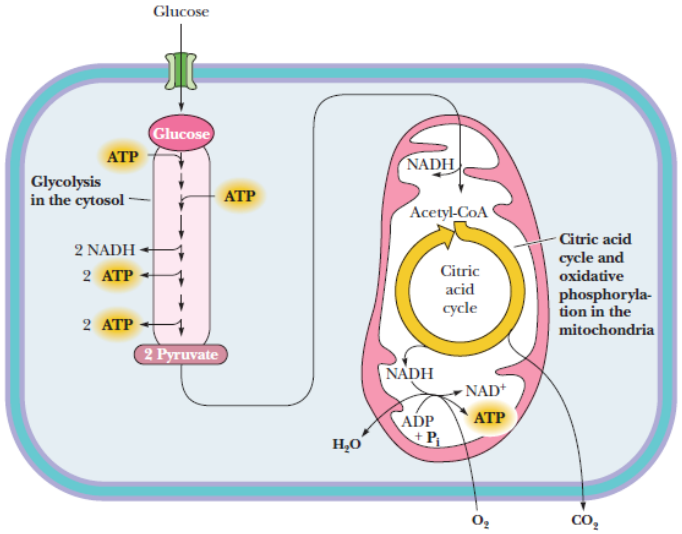


FIGURE 17.17 Compartmentalization of glycolysis, the citric acid cycle, and oxidative phosphorylation.