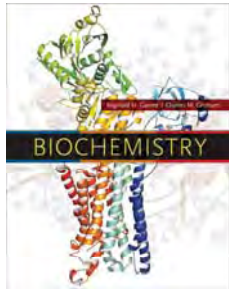
Chapter 17



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Metabolism: An Overview

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Before the class

- Is all life organism shared the same metabolic pathway?
- What are the anabolic and catabolic processes that satisfy the metabolic needs of the cell?

Outline

- Part 1: Introduciton of metabolism
  - Is metabolism similar in different organisms?
  - What can be learned from metabolic maps?
  - How do anabolic and catabolic processes form the core of metabolic pathways?
- Part 2: Energy flow and experimental tools
  - What experiments can be used to elucidate metabolic pathways?
  - What can the metabolome tell us about a biological system?
  - What food substances form the basis of human nutrition?

17.1 Is Metabolism Similar in Different Organisms?

- Remarkable similarity in major metabolic pathways
  - An evidence that all life descended from a common ancestral form
- And yet, living things also exhibit metabolic diversity

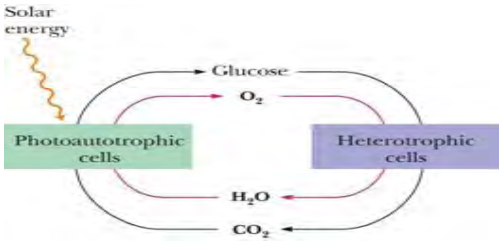
TABLE 17.1 Metabolic Classification of Organisms According to Their Carbon and Energy Requirements

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

Autotrophs use CO_2; Heterotrophs use organic carbon; Phototrophs use light; Chemotrophs use organic and inorganic electron donors

Energy Source for Life

- The Sun is Energy for Life
  - Phototrophs use light to drive synthesis of organic molecules
  - Heterotrophs use these as building blocks
  - CO_2, O_2, and H_2O are recycled

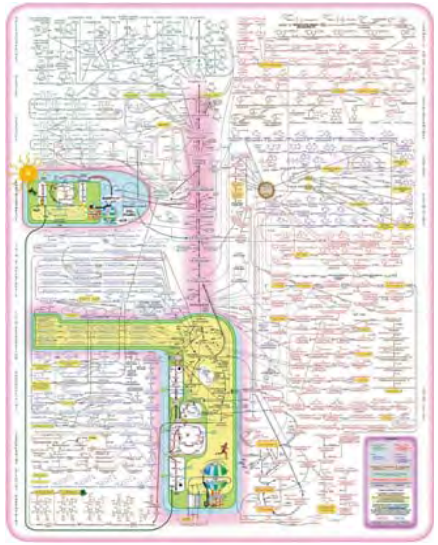


17.2 What Can Be Learned From Metabolic Maps?

- Metabolism consists of catabolism and anabolism
- Catabolism: degradative pathways
  - Usually energy-yielding
- Anabolism: biosynthetic pathways
  - Usually energy-requiring

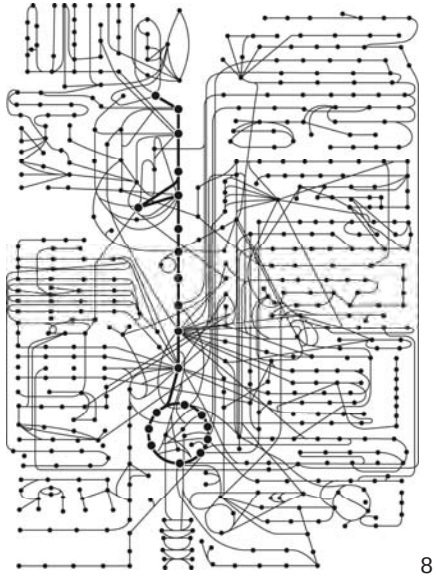
Metabolic Maps

- We will learn them all!
- More than 500 different chemical intermediates, or metabolites, and a greater number of enzymes are here.
- When the major metabolic routes are know and functions are understood, the maps become easy to follow, in spite of their complexity



Another form of Metabolic Map

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



Look at the Metabolic Maps in another way

- Represents each intermediate as a black dot and each enzyme as a line
- In this way, more than a thousand enzymes and substrates are represented by just two symbols
  - A dot connected to a single line must be a nutrient, a storage form, an end product, or an excretory product
  - A dot connected to just two lines is probably an intermediate in one pathway and has only one fate in metabolism
  - A dot connected to three represents an intermediate that has two metabolic fates

Statistic Analysis of Metabolic Maps

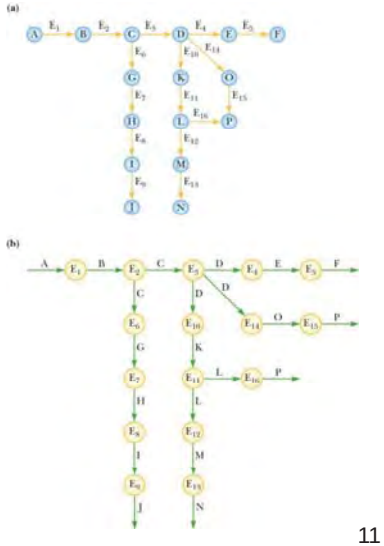
TABLE 17.2 Number of Dots (Intermediates) in the Metabolic Map of Figure 17.2, and the Number of Lines Associated with Them

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

Usually with Regulatory enzymes

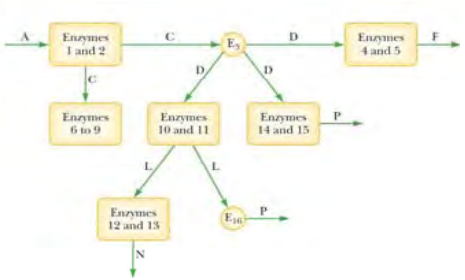
New Point of view in Metabolic Maps

- The traditional view of a metabolic pathway is metabolite-centric.
- Julia Gerrard has proposed that a protein-centric view is more informative for some purposes.



System Biology

- Protein-centric view where proteins in the pathway form multifunctional complexes.
- New tools in
  - Genomics
  - Transcriptomics
  - Proteomics
  - Metabolomics



Organization in Pathways

- Since pathways consist of sequential steps, how a serious of enzyme work together without interfering?
  - The enzymes may be separate
  - Or may form a multienzyme complex
  - Or may be a membrane-bound system
  - New research indicates that multienzyme complexes are more common than once thought

Multienzyme Systems May Take Different Forms

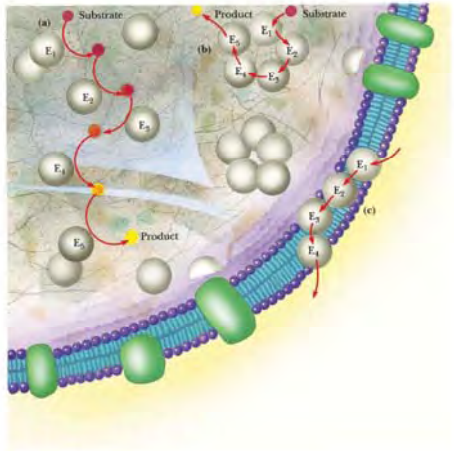


Figure 17.5 Schematic representation of types of multienzyme systems carrying out a metabolic pathway. (a) Physically separate, soluble enzymes with diffusing intermediates. (b) A multienzyme complex. Substrate enters the complex and becomes bound and then modified by E1 to E5. No intermediates are free to diffuse away. (c) A membrane-bound multienzyme system.

17.3 How Do Anabolic and Catabolic Processes Form the Core of Metabolic Pathways?

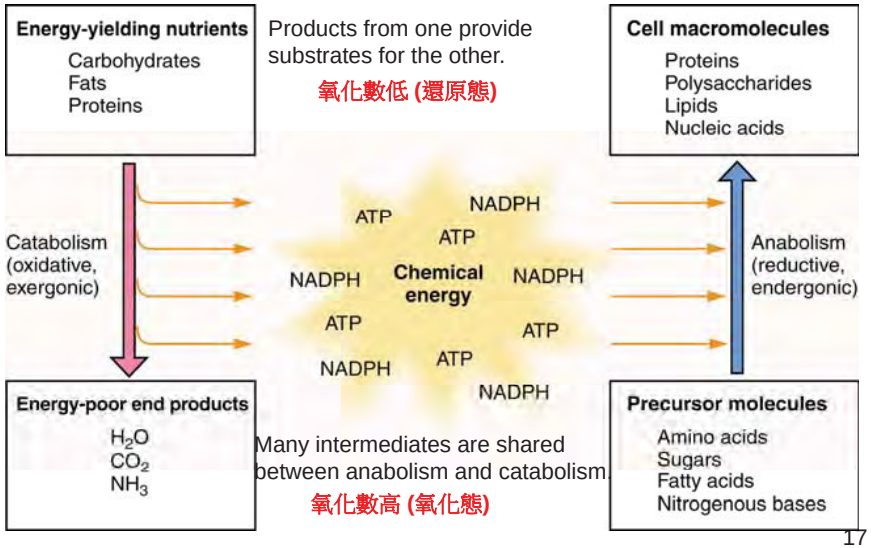
- Catabolic pathways are characteristically energy-yielding
- Anabolic pathways are characteristically energy-requiring
- Catabolism involves the oxidative degradation of complex nutrient molecules
- Anabolism is a synthetic process in which the varied and complex biomolecules are assembled from simpler precursors

Train yourself to make conclusions!

Metabolism	definition	purpose	Energy
Catabolism	Oxidative degradative pathways	Usually energy-yielding (exergonic)	ATP/ NADH
Anabolism	biosynthetic pathways	energy-requiring	ATP/ NADPH

- Oxidative phosphorylation
- Reducing power
- High-energy electrons

Energy flow in Redox reactions



Anabolism and Catabolism Are Not Mutually Exclusive

- Catabolic pathways converge to a few end products
- Anabolic pathways diverge to synthesize many biomolecules
- Some pathways serve both in catabolism and anabolism
- Such pathways are amphibolic

Comparing Pathways

- Anabolic & catabolic pathways involving the same product are not the same
- Some steps may be common to both
- Others must be different - to ensure that each pathway is spontaneous
- This also allows regulation mechanisms to turn one pathway on and the other off

Metabolic Regulation Requires Different Pathways for Oppositely Directed Metabolic Sequences

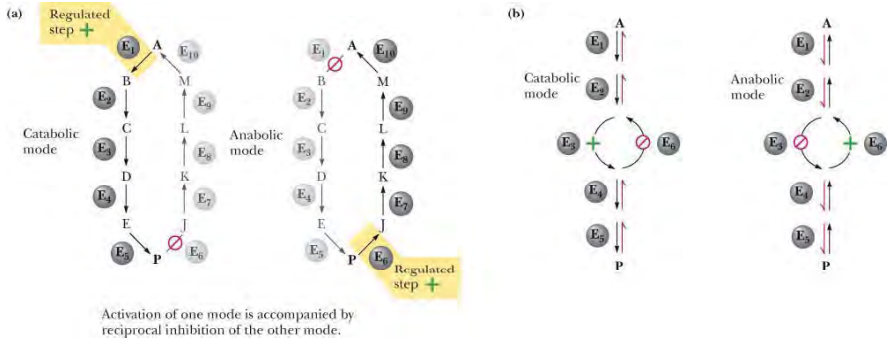


Figure 17.8 Parallel pathways of catabolism and anabolism must differ in at least one metabolic step in order that they can be regulated independently. Shown here are two possible arrangements of opposing catabolic and anabolic sequences between A and P. (a) Parallel sequences proceed by independent routes. (b) Only one reaction has two different enzymes.

End of Part 1

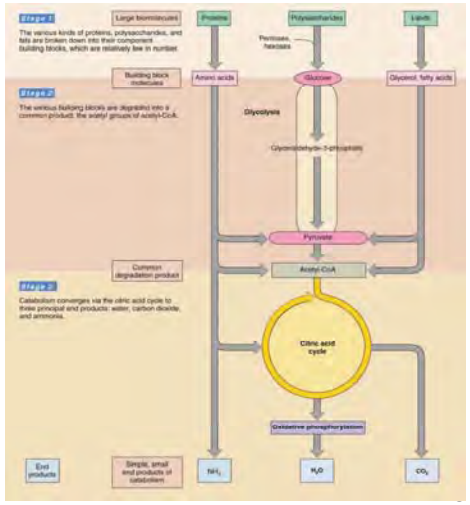
- Ask yourself…
  - What is catabolism?
  - What is anabolism?
  - What information are we learned from metabolic maps?

17.6 What Food Substances Form the Basis of Human Nutrition?

- **Protein** is a rich source of nitrogen and also provides essential amino acids
- **Carbohydrates** provide needed energy and essential components for nucleotides and nucleic acids
- **Lipids** provide essential fatty acids that are key components of membranes and also important signal molecules
- **Fiber** – whether soluble or insoluble – can be a beneficial complement in the human diet

The Pathways of Catabolism Converge to a Few End Products

- The three stages of catabolism.
  - **Stage 1**: Proteins, polysaccharides, and lipids are broken down into building blocks.
  - **Stage 2**: The building blocks are degraded into the common product (acetyl-CoA).
  - **Stage 3**: Catabolism converges to three principal end products: water, carbon dioxide, and ammonia.

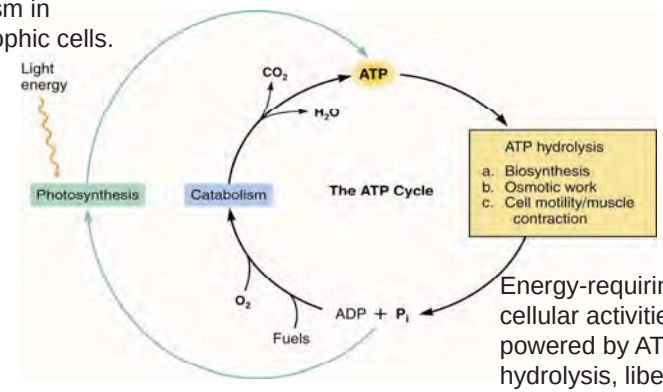


ATP Serves in a Cellular Energy Cycle

- ATP is the energy currency of cells
- Phototrophs transform light energy into the chemical energy of ATP
- In heterotrophs, catabolism produces ATP, which drives activities of cells
- ATP cycle carries energy from photosynthesis or catabolism to the energy-requiring processes of cells

The ATP Cycle in Cells

ATP is formed via photosynthesis in phototrophic cells or catabolism in heterotrophic cells.



Energy-requiring cellular activities are powered by ATP hydrolysis, liberating ADP and P_i.

Redox in Metabolism

- NAD^+ collects high-energy electrons ($H:^-$) released in catabolism
- NADH = energy shuttle
- Anabolism is reductive - NADPH provides the reducing power (electrons) for anabolic processes
- NADPH = electron carrier

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The Substrates of Catabolism Contain Relatively Reduced Forms of Carbon

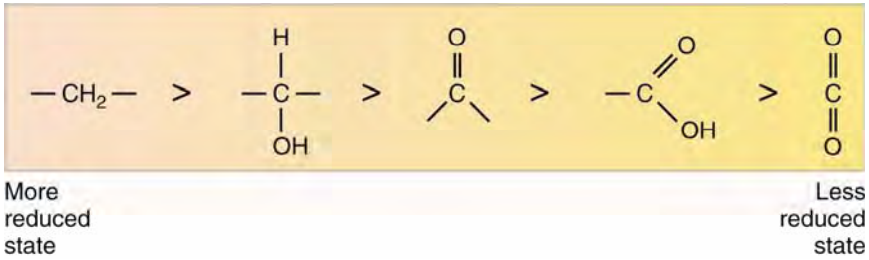


Figure 17.10 Comparison of the state of reduction of carbon atoms in biomolecules. Chains of $–CH_2-$ groups are the most practical form of reduced carbon in the biosphere. Carbon dioxide is the final product of catabolism and the most oxidized form of carbon in the biosphere.

NAD^+ Collects Electrons Released in Catabolism

- The substrates of catabolism – proteins, carbohydrates, and lipids – are good sources of chemical energy because their carbon is reduced
- The oxidative reactions of catabolism release reducing equivalents from these substrates, often in the form of hydride ions
- These hydrides are transferred to NAD^+ molecules, reducing them to NADH
- NADH in turn passes these reducing equivalents to other acceptors
- The ultimate oxidizing agent, O_2, is the final acceptor of electrons, becoming reduced to H_2O

NAD^+ Collects Electrons Released in Catabolism

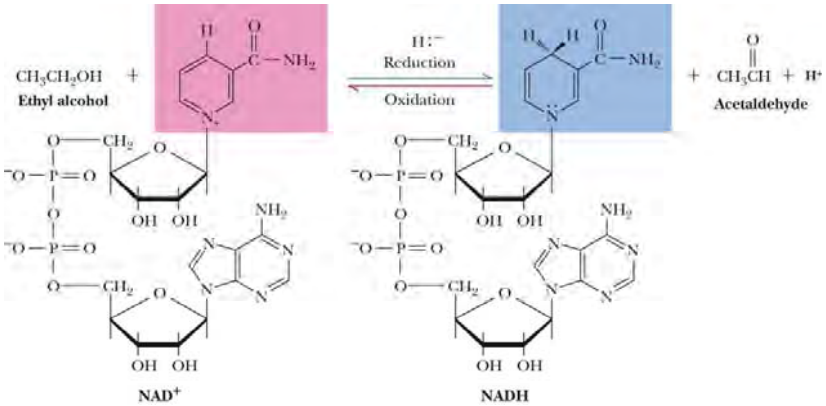


Figure 17.11 Hydrogen and electrons released in the course of oxidative catabolism are transferred as hydride ions to the pyridine nucleotide, NAD^+, to form NADH + H^+ in dehydrogenase reactions.

NADPH Provides the Reducing Power for Anabolic Processes

- Whereas catabolism is oxidative, anabolism is reductive
- Biosynthesis is typically reductive and requires reducing equivalents – from NADPH
- NADPH can be viewed as the carrier of electrons from catabolic reactions to anabolic reactions
- In photosynthesis, light energy is used to pull electrons from water and transfer them to $NADP^+$
- O_2 is a by-product of this process

NADPH Provides the Reducing Power for Anabolic Processes

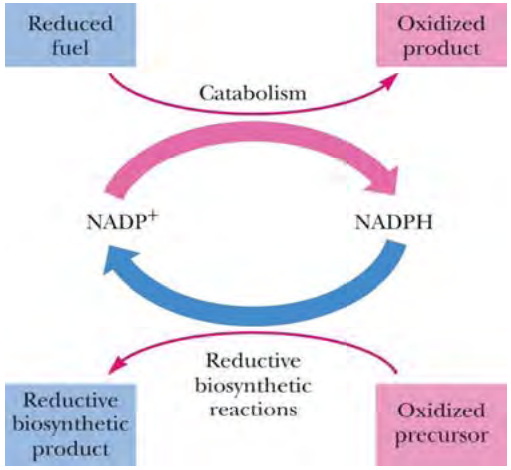


Figure 17.12 Transfer of reducing equivalents from catabolism to anabolism via the NADPH cycle.

Other Vitamins and Coenzymes Discussed Elsewhere in the Textbook

TABLE 17.1 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 (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	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	25
	Methylcobalamin		
Biotin	Biotin–lysine complexes (biocytin)	Carrier of carboxyl groups in carboxylation reactions	22, 24
Lipoic acid	Lipoyl–lysine complexes (lipoamide)	Coupling acyl group transfer and electron transfer during oxidation and decarboxylation of α-keto acids	19
Folic acid	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)			

17.4 What Experiments Can Be Used to Elucidate Metabolic Pathways?

- Eduard Buchner (late 19th century) showed that fermentation of glucose in yeast cells yielded ethanol and carbon dioxide
- This led to a search for intermediates of glucose breakdown
- Metabolic inhibitors were important tools for elucidating the pathway steps.
- Mutations also were used to create specific metabolic blocks

17.4 What Experiments Can Be Used to Elucidate Metabolic Pathways?

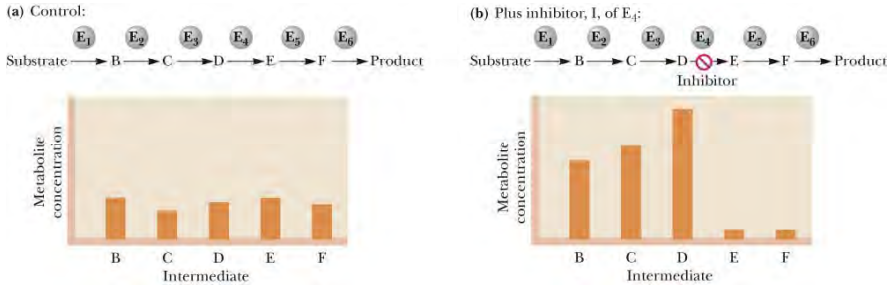


Figure 17.13 The use of inhibitors to reveal the sequence of reactions in a metabolic pathway. (a) Control. (b) Plus inhibitor. Intermediates upstream of the metabolic block (B, C, and D) accumulate, revealing themselves as intermediates in the pathway. The concentration of intermediates lying downstream (E and F) will fall.

Isotopic Tracers Can Be Used as Metabolic Probes

- Metabolic pathways have been elucidated by use of isotopic forms of elements
- Metabolic substrates and intermediates can be "labeled" with a measurable isotope and then "traced" through a series of reactions
- Two types of isotopes have been used in this way
  - Radioactive isotopes, such as ^{14}C and ^{32}P
  - Stable "heavy" isotopes, such as ^{18}O and ^{15}N

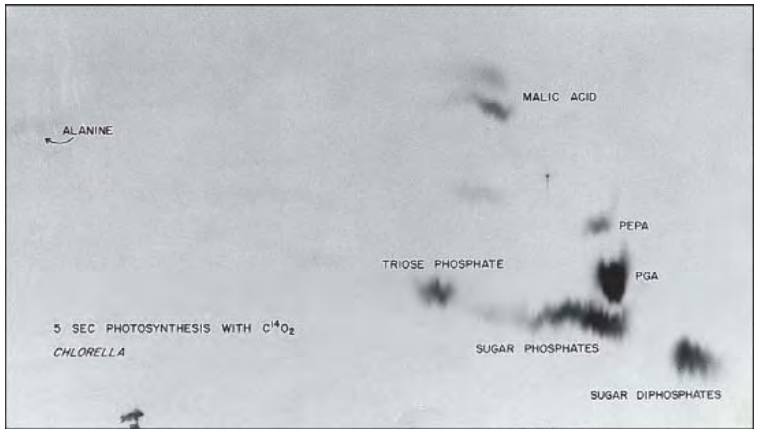
Isotopic Tracers Can Be Used as Metabolic Probes

TABLE 17.4 Properties of Radioactive and Stable "Heavy" Isotopes Used as Tracers in Metabolic Studies

Isotope	Type	Radiation Type	Half-Life	Relative Abundance*
^{2}H	Stable			0.0154%
^{3}H	Radioactive	β^-	12.1 years	
^{13}C	Stable			1.1%
^{14}C	Radioactive	β^-	5700 years	
^{15}N	Stable			0.365%
^{18}O	Stable			0.204%
^{24}Na	Radioactive	β^-, γ	15 hours	
^{32}P	Radioactive	β^-	14.3 days	
^{35}S	Radioactive	β^-	87.1 days	
^{36}Cl	Radioactive	β^-	310,000 years	
^{42}K	Radioactive	β^-	12.5 hours	
^{45}Ca	Radioactive	β^-	152 days	
^{59}Fe	Radioactive	β^-, γ	45 days	
^{131}I	Radioactive	β^-, γ	8 days	

Isotopic Tracers Can Be Used as Metabolic Probes

Figure 17.14
One of Melvin Calvin's early experiments using a radioactive isotope as a metabolic tracer. 3-Phosphoglycerate (PGA) is labeled when algae are incubated with radioactive CO_2.



NMR Spectroscopy is a Noninvasive Metabolic Probe

- The nuclei of certain atomic isotopes have **magnetic moments**
- Such nuclei can absorb radio-frequency energy in the presence of a magnetic field at a unique **resonant frequency**
- The nuclear magnetic resonance (NMR) absorption is influence in predictable ways by the chemical nature of its neighboring atoms and by its dynamic behavior (motion)
- For these reasons, NMR signals can provide a wide range of structural and dynamic information about biomolecules

NMR Spectroscopy is a Noninvasive Metabolic Probe

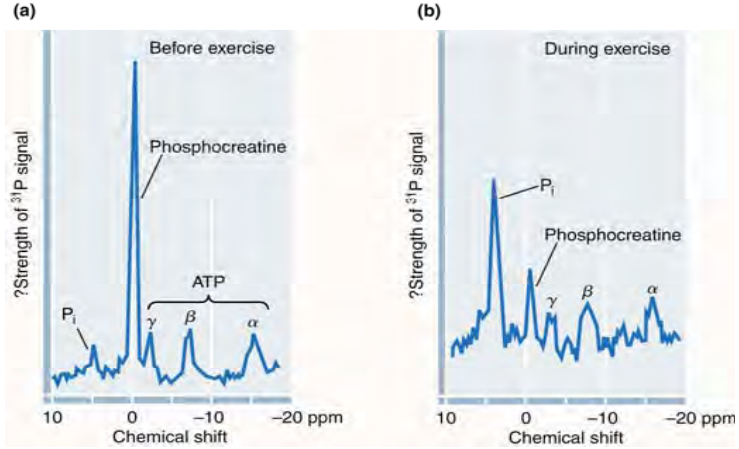


Figure 17.15 The metabolism of a living subject can be observed in real time with NMR spectroscopy.

Metabolic Pathways are Compartmentalized Within Cells

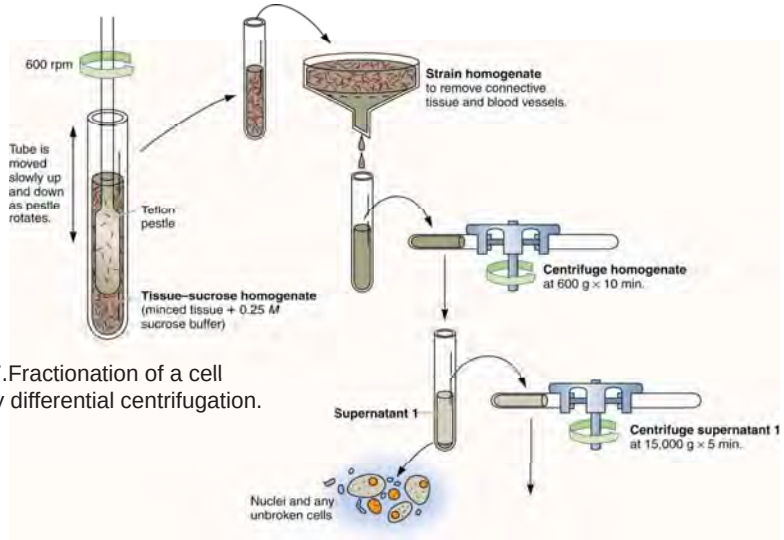
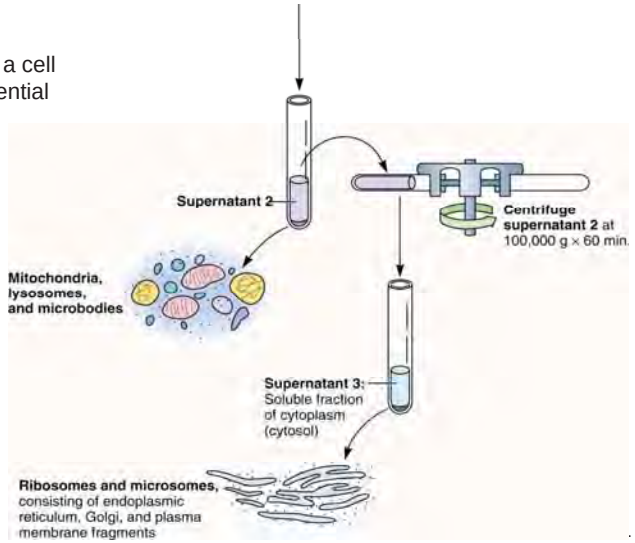


Figure 17.Fractionation of a cell extract by differential centrifugation.

Metabolic Pathways are Compartmentalized Within Cells

Figure17.
Fractionation of a cell extract by differential centrifugation.



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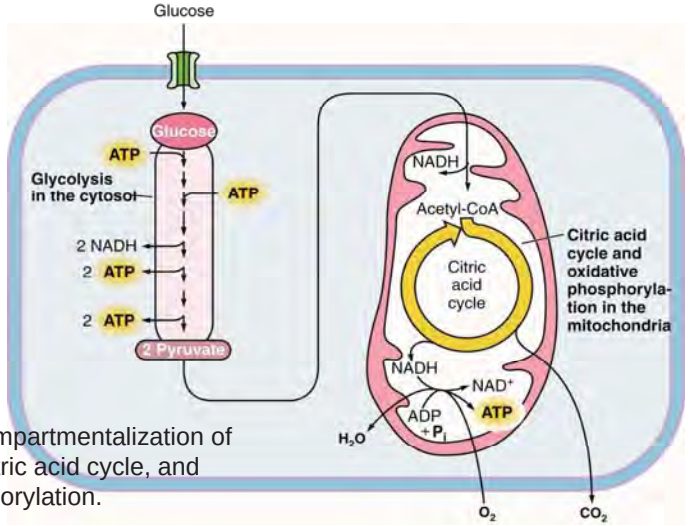
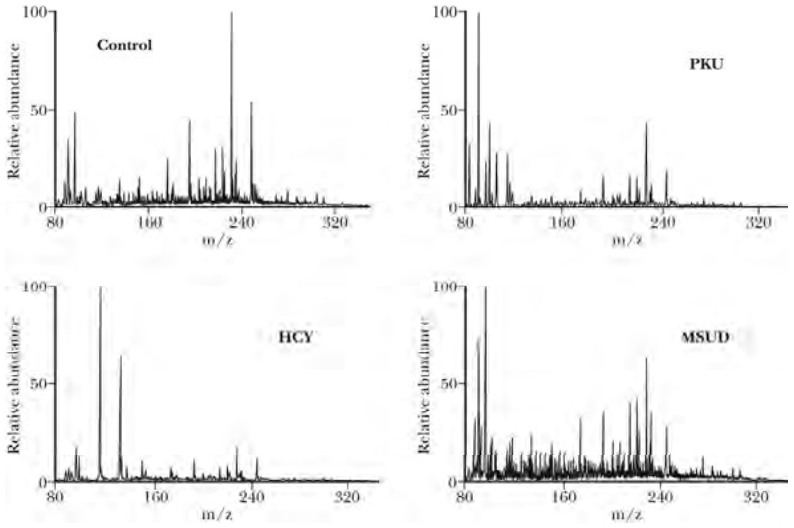


Figure 17.17 Compartmentalization of glycolysis, the citric acid cycle, and oxidative phosphorylation.

17.5 What Can the Metabolome Tell Us About a Biological System?

- The **metabolome** is the complete set of low-molecular weight molecules present in an organism or excreted by it under a given set of circumstances
- **Metabolomics** is the systematic identification and quantitation of all these metabolites in a given organism or sample
- **Mass spectrometry (MS)** and **nuclear magnetic resonance (NMR)** are both powerful techniques for metabolomic analysis
- **MS** offers unmatched sensitivity for detection of metabolites at low concentrations
- **NMR** provides remarkable resolution and discrimination of metabolites in complex mixtures

Figure 17.18 Mass spectrometry offers remarkable sensitivity for metabolomic analyses.



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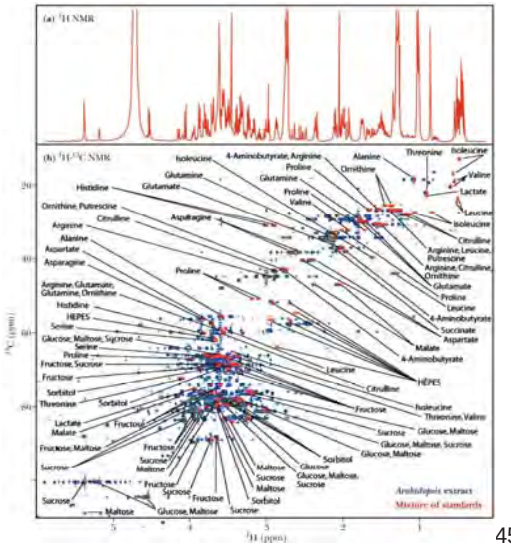

Figure 17.19 NMR provides remarkable resolution and discrimination of metabolites in complex mixtures.

End of Part2

- Ask yourself…
  - What are the 3 stages of catabolism?
  - What are the energy flows in cells?
  - How cells storage their energy?
  - How to study a metabolic pathway?

End of the class

- You should have learned…
  - Energy flow in the biosystem and inside cells
  - 3 common stages of catabolism
  - How to produce high energy electrons in cells?
  - How cells storage high energy electrons?
  - How cells use high energy electrons?