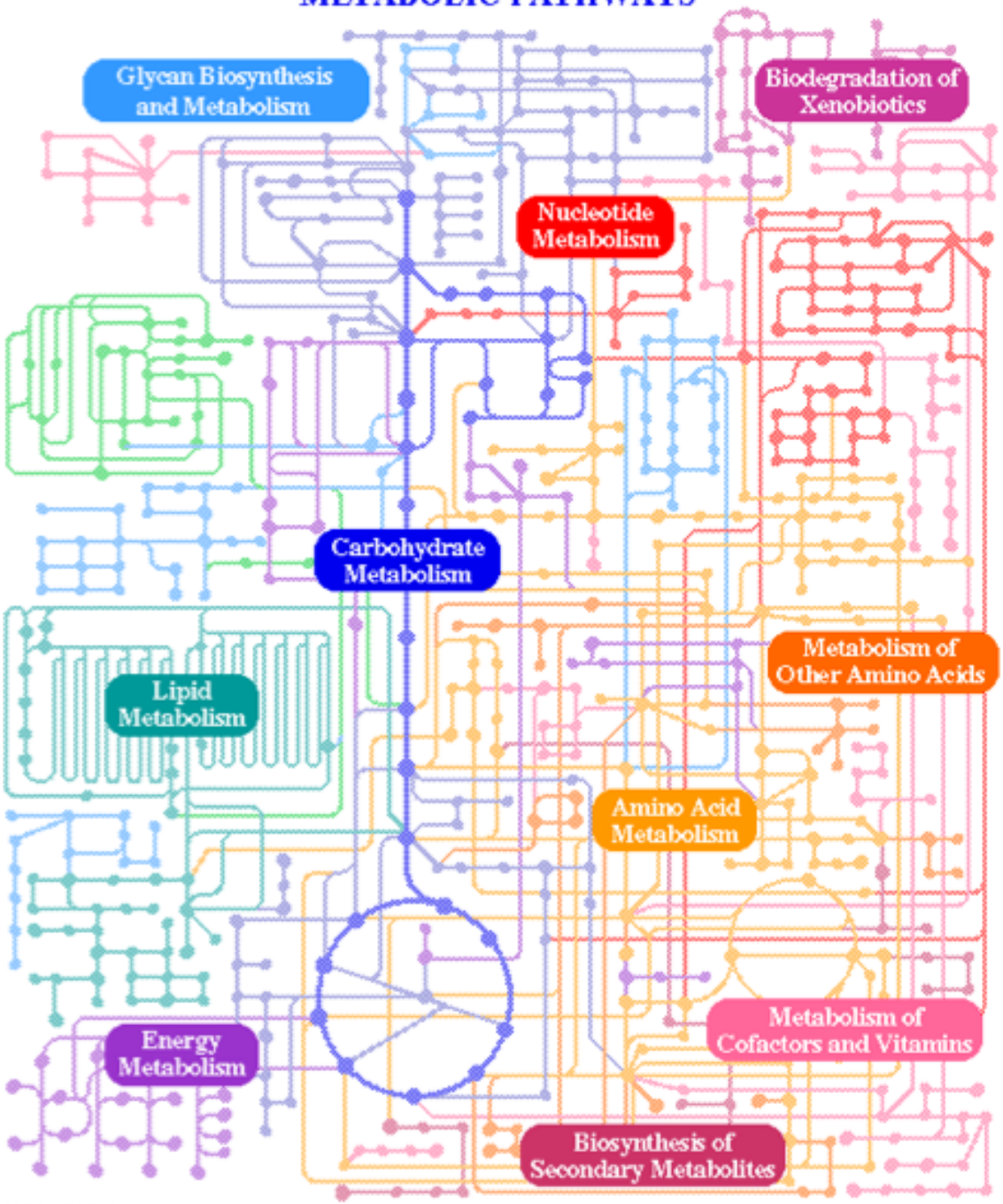
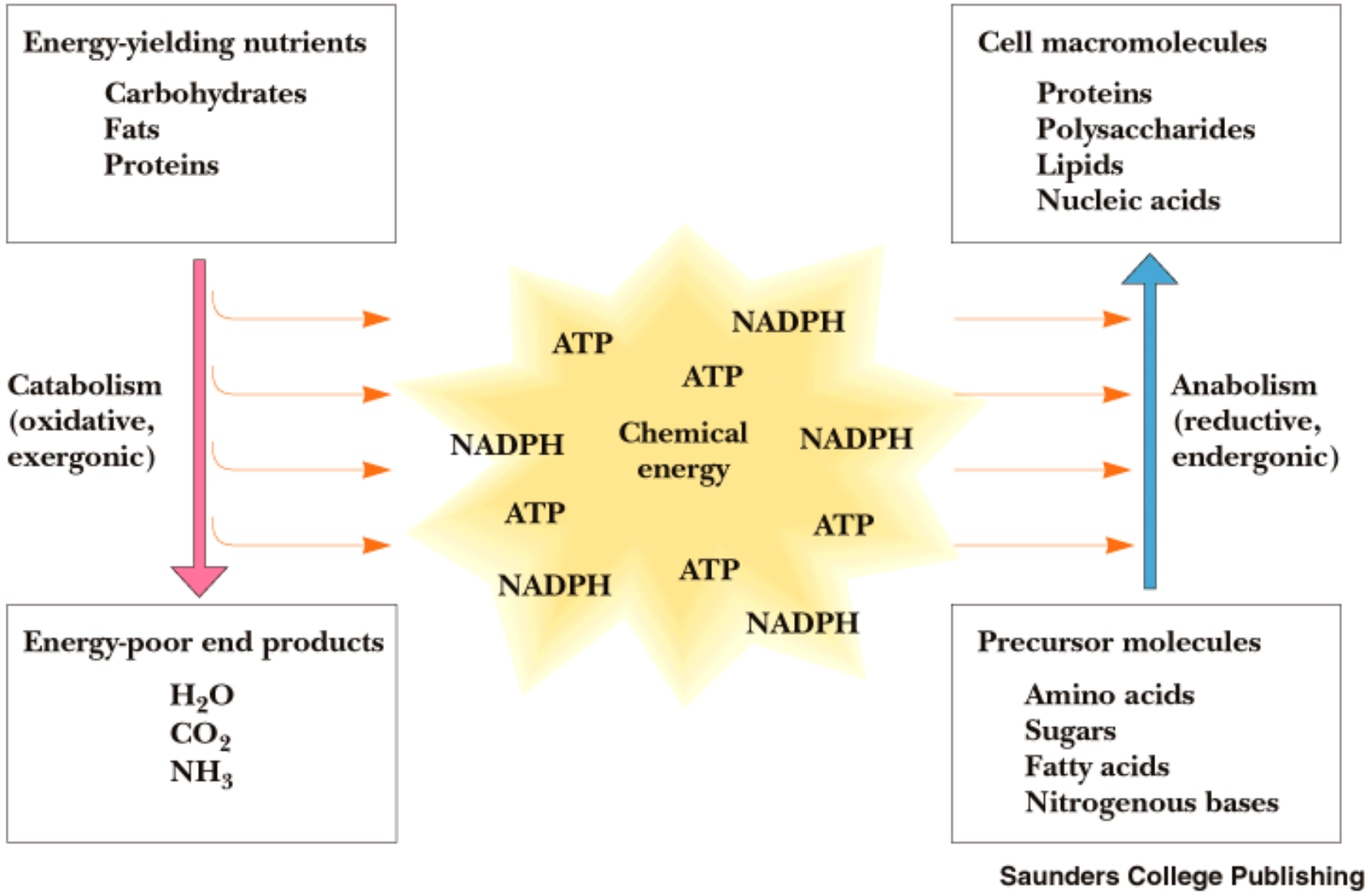
1. METABOLIC REGULATION: GENERAL CONCEPTS

METABOLIC PATHWAYS



OVERVIEW

Figure 18.4



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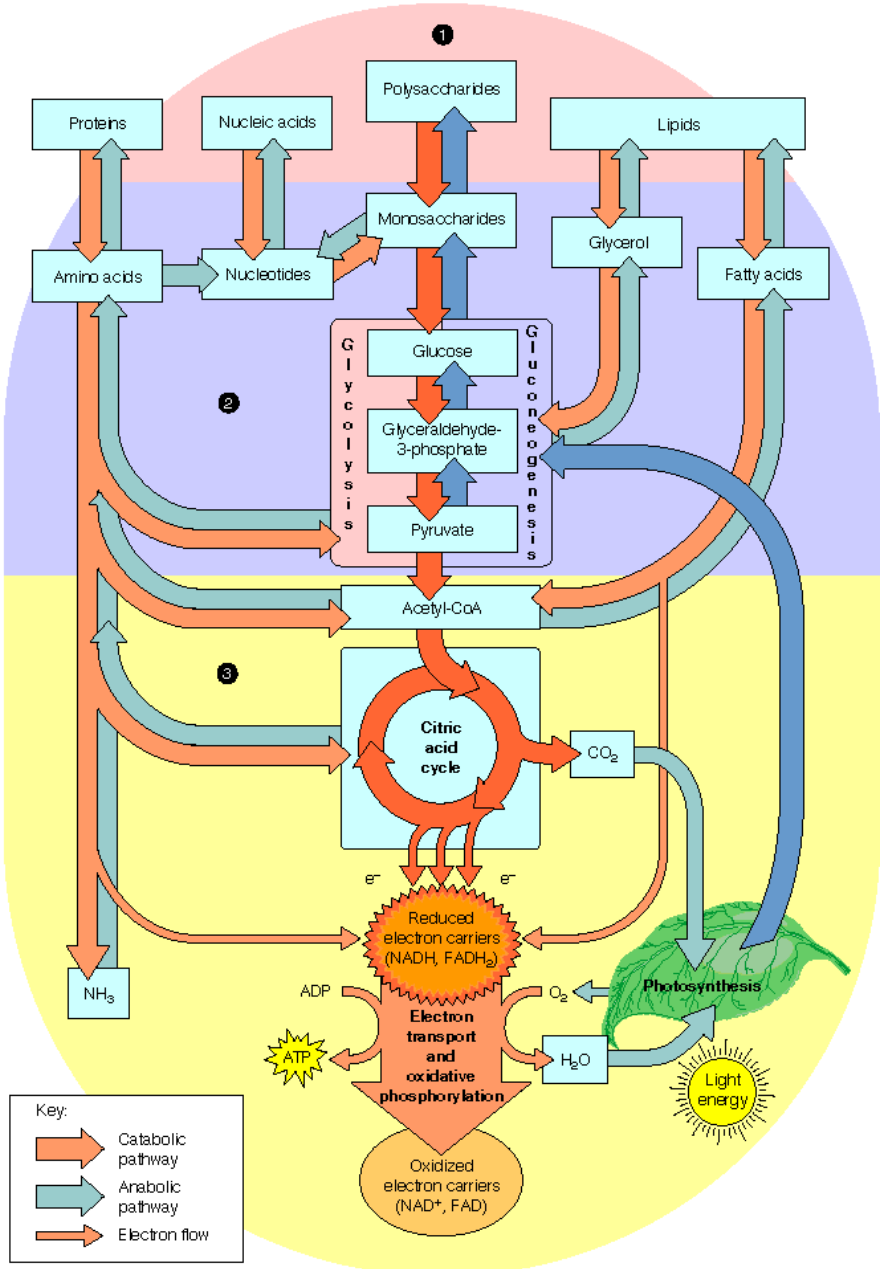
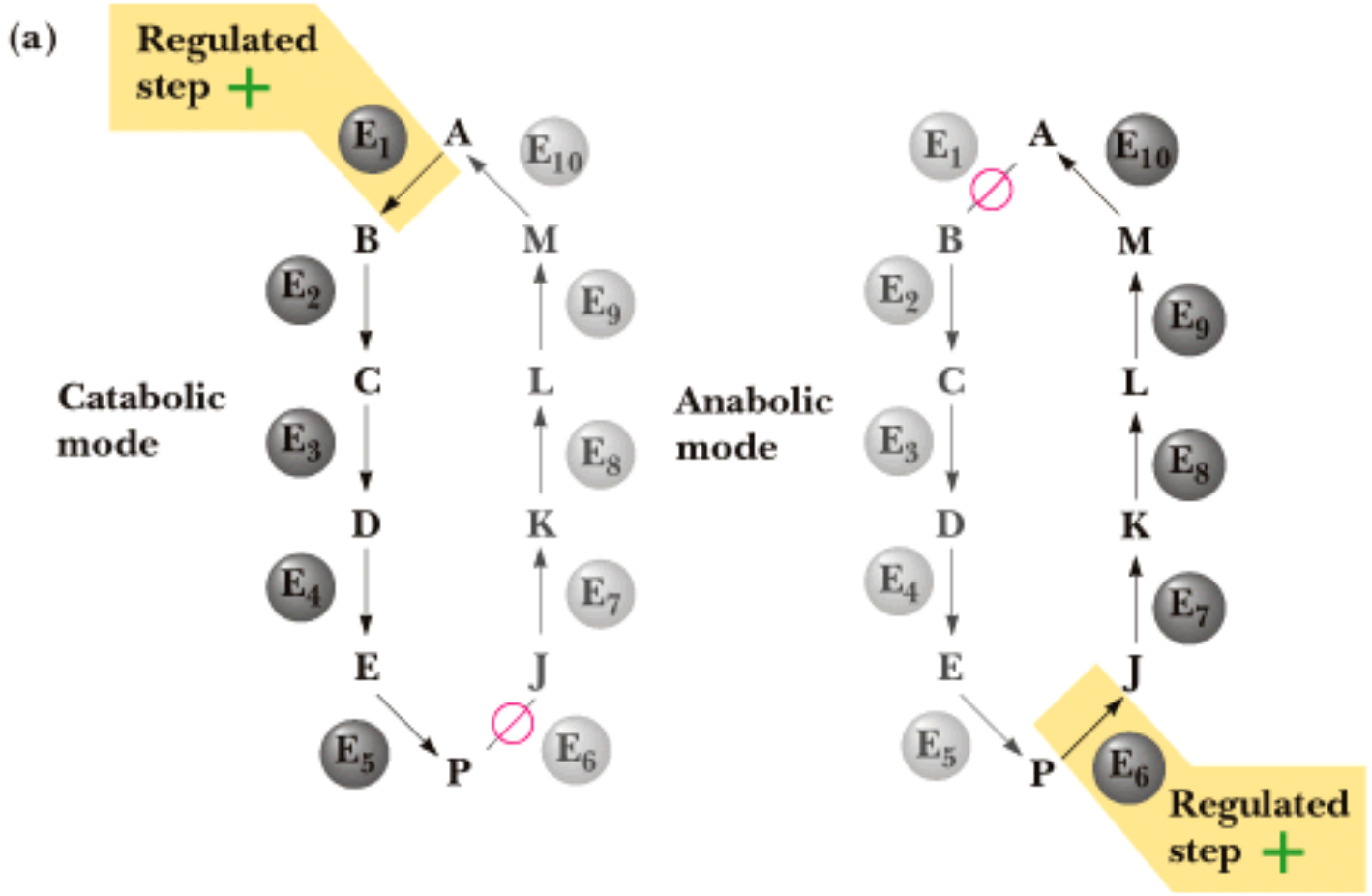
OVERVIEW

- 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**
- Pathways consist of sequential steps
- The enzymes may be separate
- Or may form a multi-enzyme complex
- Or may be a membrane-bound system
- New research indicates that multi-enzyme complexes are more common than once thought

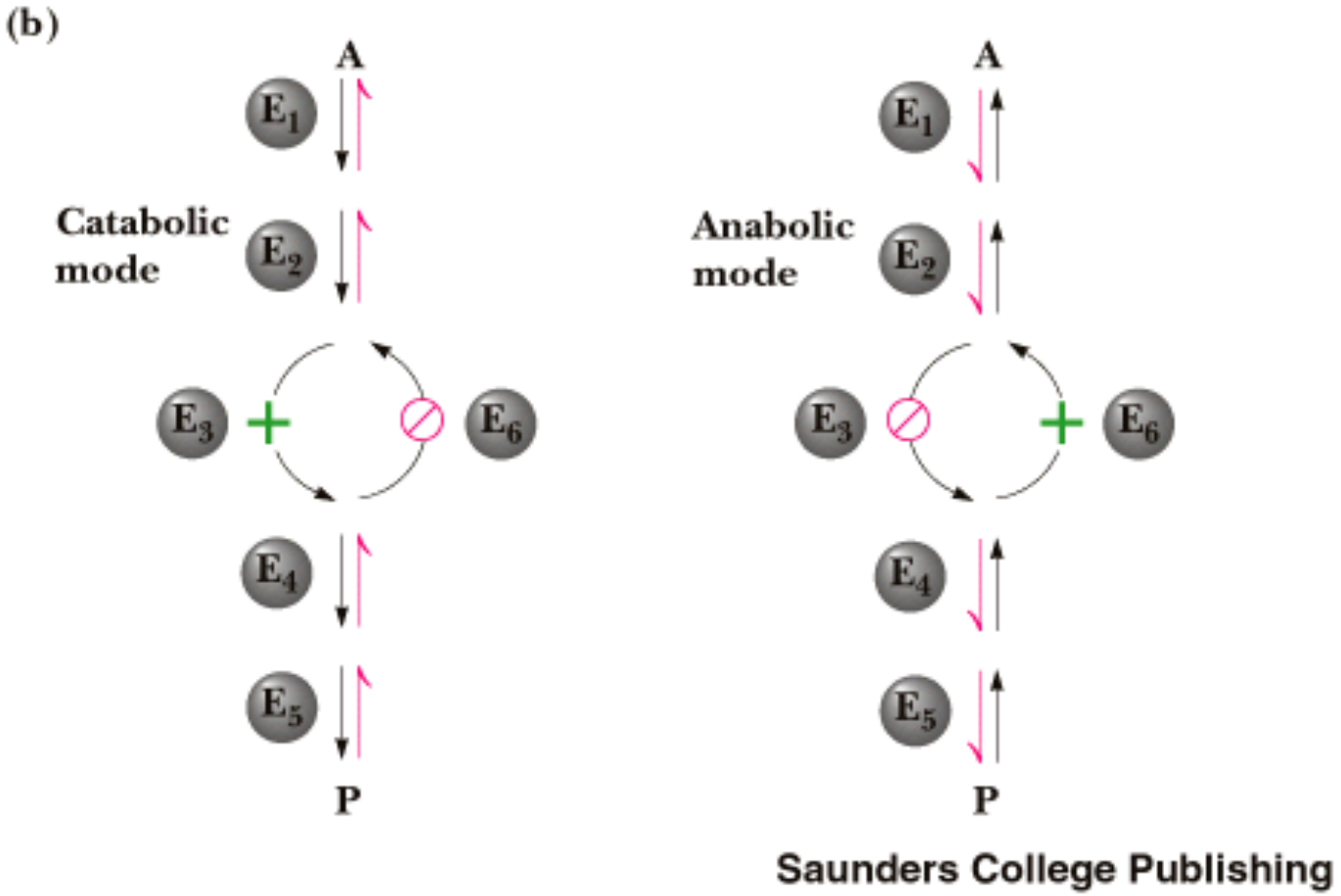


OVERVIEW



Activation of one mode is accompanied by reciprocal inhibition of the other mode.

OVERVIEW


(b)
A
E1
Catabolic mode
E2
E3
E6
E4
E5
P
A
E1
Anabolic mode
E2
E3
E6
E4
E5
P
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OVERVIEW

Table 14.1

Contrasting characteristics of catabolism and anabolism

Catabolism
Leads to degradation of biomolecules
Overall process of chemical oxidation and formation of reduced cofactors of NADH, NADPH, $FADH_2$
Release of chemical energy (exergonic) and production of ATP from ADP
Convergence of pathways
Anabolism
Synthesis of biomolecules
Overall process of chemical reduction and formation of oxidized cofactors NAD^+, $NADP^+$, FAD
Requirement for energy input (endergonic) and use of ATP
Divergence of pathways

Table 14-1 Concepts in Biochemistry, 3/e

OVERVIEW

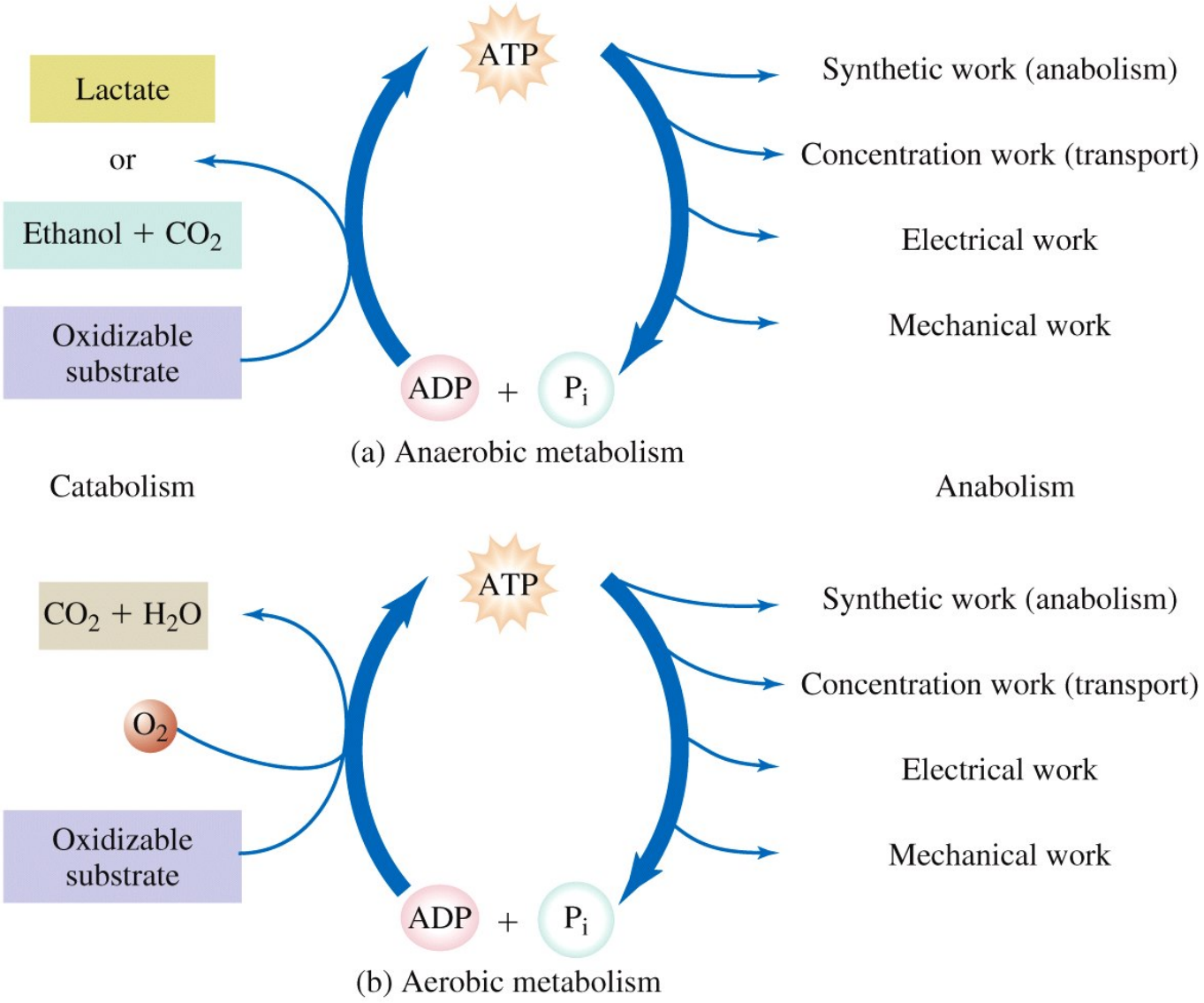
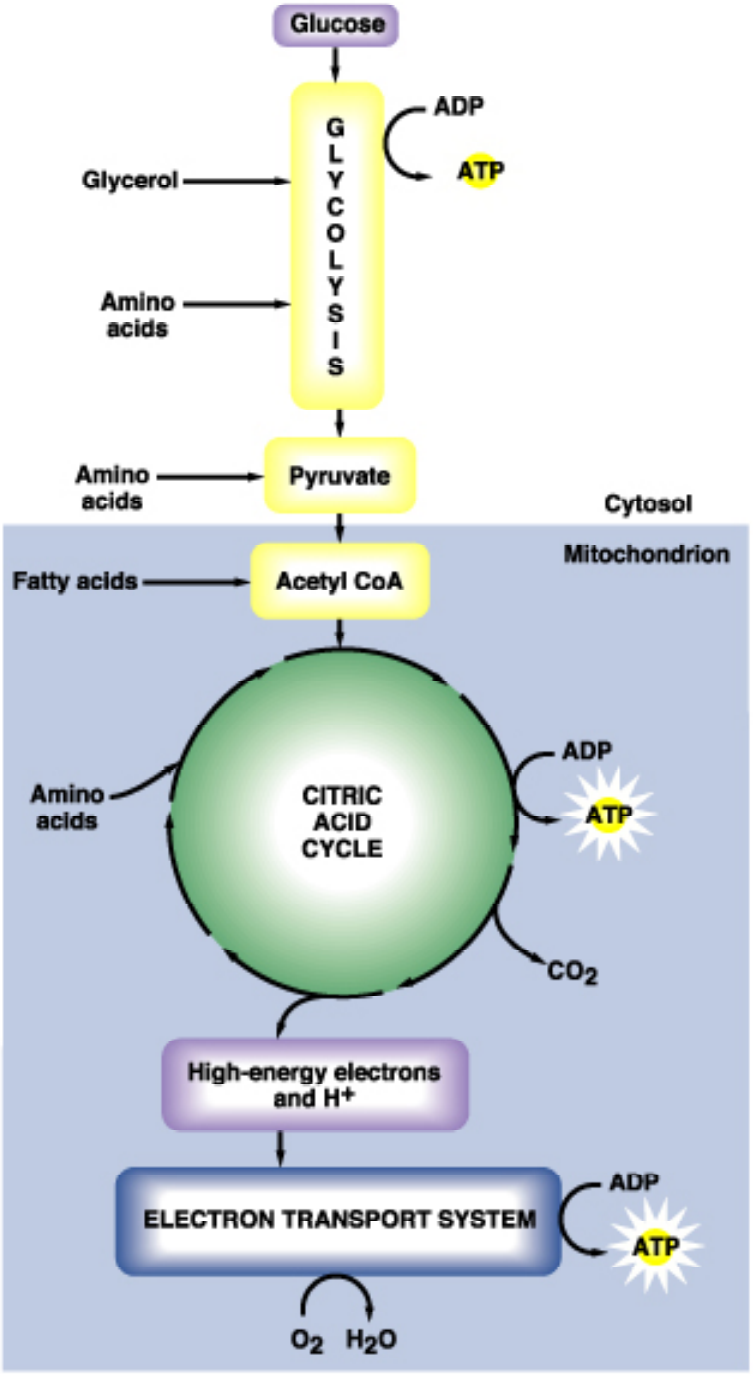


Figure 14-5 Concepts in Biochemistry, 3/e

OVERVIEW


Glucose
GLYCOLYSIS
ADP
ATP
Glycerol
Amino acids
Amino acids
Pyruvate
Cytosol
Mitochondrion
Fatty acids
Acetyl CoA
Amino acids
CITRIC ACID CYCLE
ADP
ATP
CO_2
High-energy electrons and H^+
ELECTRON TRANSPORT SYSTEM
ADP
ATP
O_2 H_2O

ENZYMES

Table 14.2

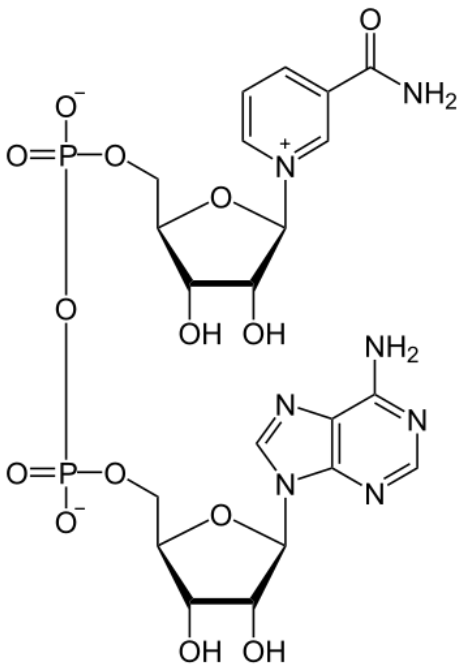
Types of chemical reactions in metabolism correlated to enzyme classes

Type of Reaction	Enzyme Class	Description of Reaction
1. Oxidation–reduction	Oxidoreductases (dehydrogenases)	Transfer of electrons
2. Group transfer	Transferases	Transfer of a functional group from one molecule to another or within a single molecule
3. Hydrolytic cleavage (hydrolysis)	Hydrolases	Cleavage of bonds by water (transfer of functional groups to water)
4. Nonhydrolytic cleavage	Lyases	Splitting a molecule by nonhydrolytic processes
5. Isomerization and rearrangement	Isomerases	Rearrangement of functional groups to form isomers
6. Bond formation using energy from ATP	Ligases	Formation of carbon–carbon and other bonds with energy from ATP

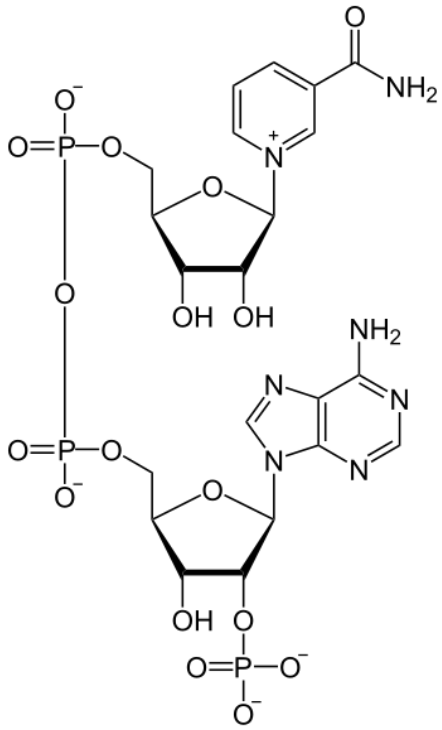
Table 14-2 Concepts in Biochemistry, 3/e

REDOX IN METABOLISM

- NAD^+ collects electrons released in catabolism
- Catabolism is oxidative - substrates lose reducing equivalents, usually H^- ions
- Anabolism is reductive - NADPH provides the reducing power (electrons) for anabolic processes

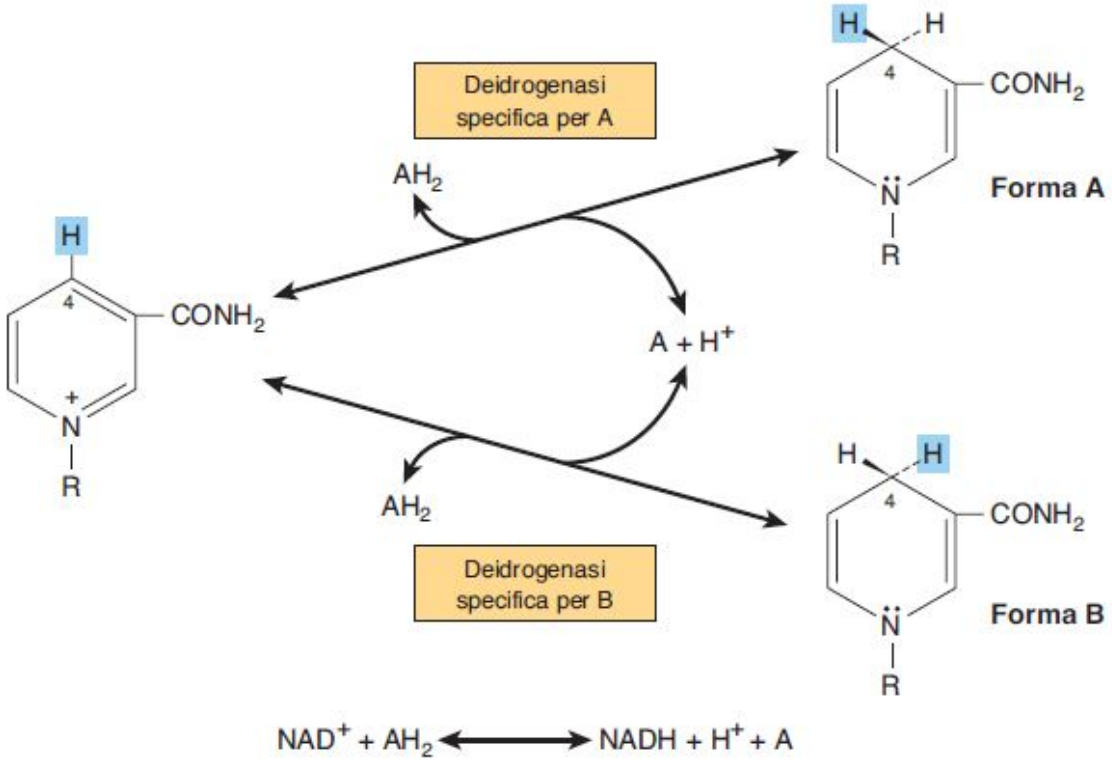


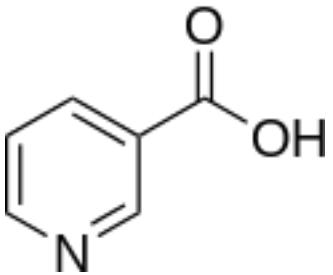
Nicotinamide adenine dinucleotide



Nicotinamide adenine dinucleotide phosphate

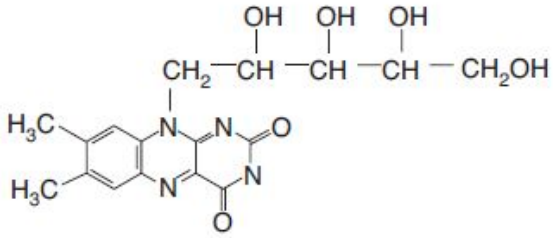
REDOX IN METABOLISM



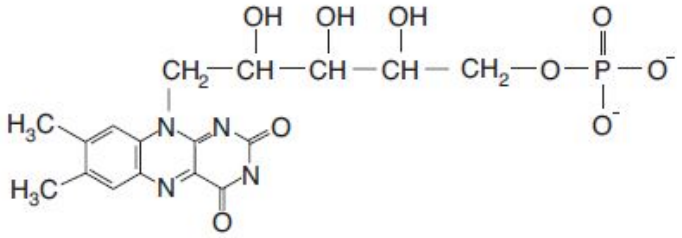


Niacin or vitamin B_3

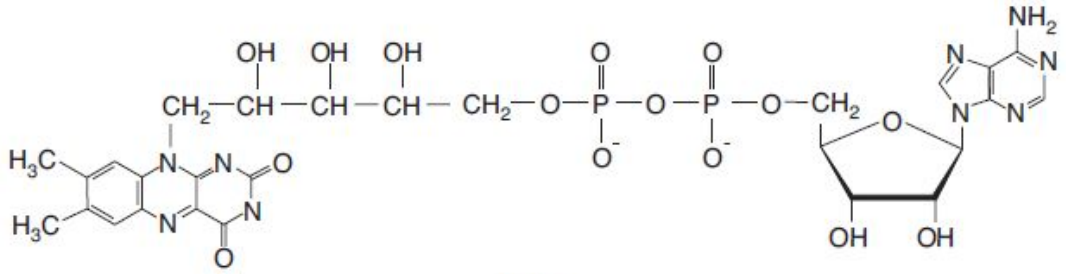
Redox in Metabolism: FMN and FAD



Riboflavina



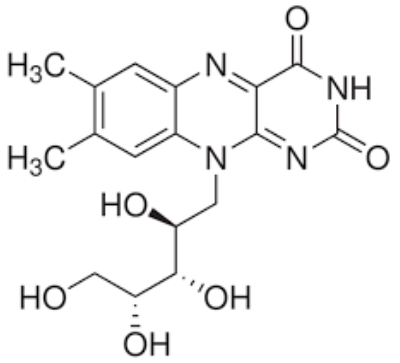
FMN



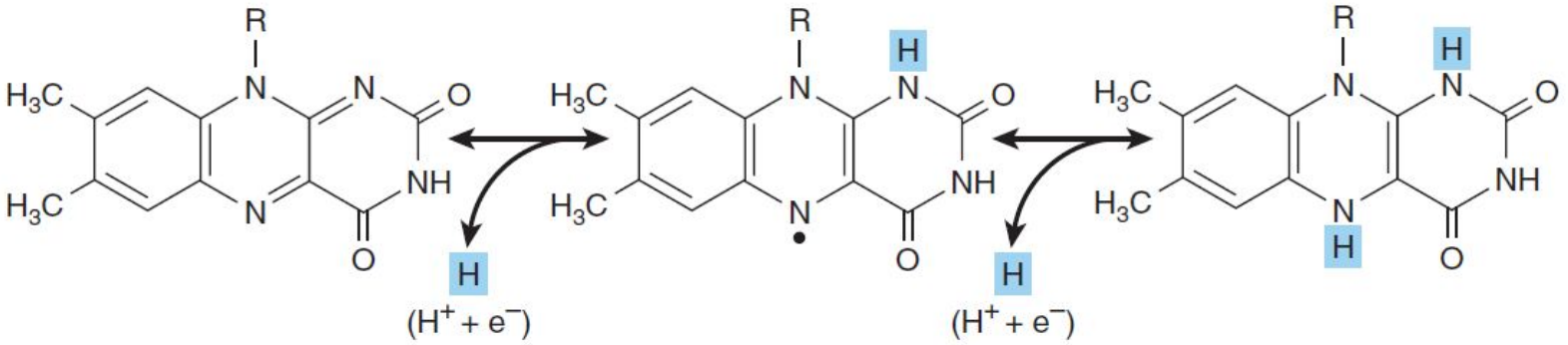
FAD

FMN: Flavin mononucleotide
FAD: Flavin adenine dinucleotide

Riboflavin or vitamin B_2



Redox in Metabolism: FMN and FAD



REDOX IN METABOLISM

Table 14.3

Relative oxidation levels of carbon in functional groups

Functional Group[a,b]	Name	Geometry of Carbon Center	Relative Oxidation Level
CH_4	Methane	Tetrahedral	Lowest
CH_3-	Methyl	Tetrahedral	
$\begin{array}{l}CH_2-\\ \vert\end{array}$	Methylene	Tetrahedral	
$RHC{=}CHR'$	Methene	Planar	
$\begin{array}{l}RCHR'\\ \vert\\ OH\end{array}$	Alcohol	Tetrahedral	
$\begin{array}{l}RCH\\ \Vert\\ O\end{array}$	Aldehyde	Planar	
$\begin{array}{l}RCR'\\ \Vert\\ O\end{array}$	Ketone	Planar	
$\begin{array}{l}RCX\\ \Vert\\ O\end{array}$	Carboxylic acid or derivative	Planar	
$O{=}C{=}O$	Carbon dioxide	Planar (linear)	Highest

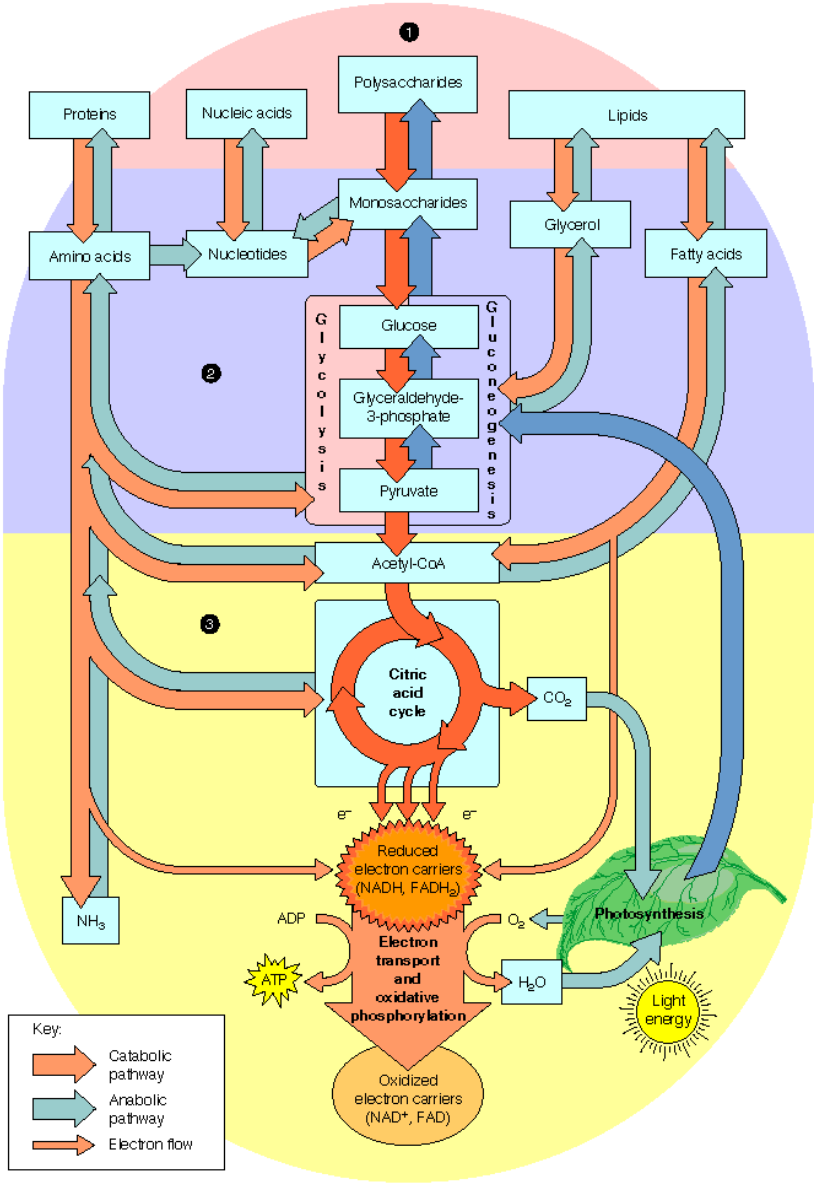
[a] The carbon center undergoing oxidation is in red.

[b] R, R′ = alkyl or aryl group; X = —OH (acid), —OR (ester), —NH_2 (amide).

Table 14-3 Concepts in Biochemistry, 3/e

MECHANISMS FOR CONTROLLING METABOLIC PATHWAYS

- Control of enzyme levels
- Control of enzyme activity
- Compartmentation
- Hormonal regulation
- Distributive control of metabolism
- Specialization of organs



Factors influencing enzymes levels and activity activity

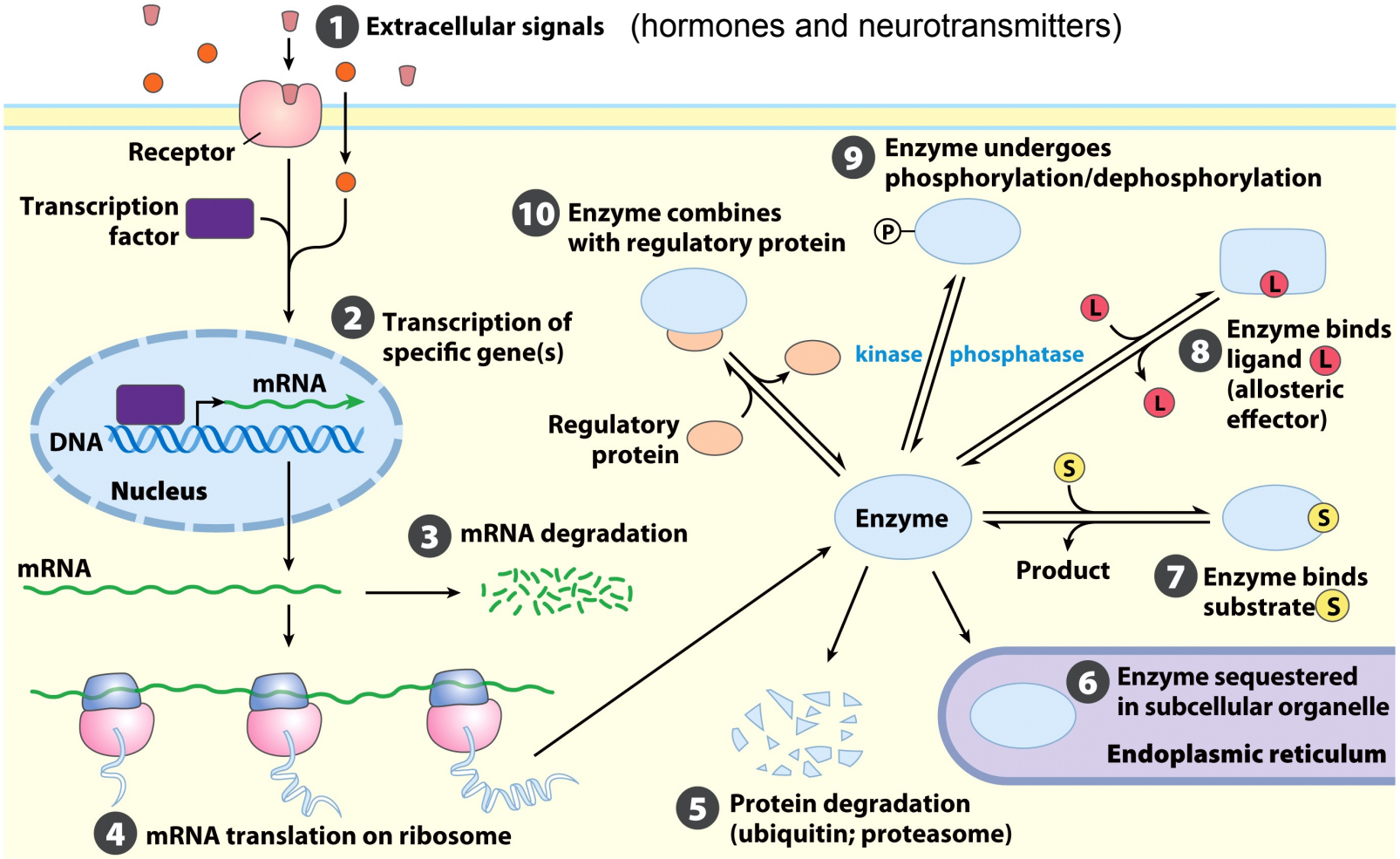
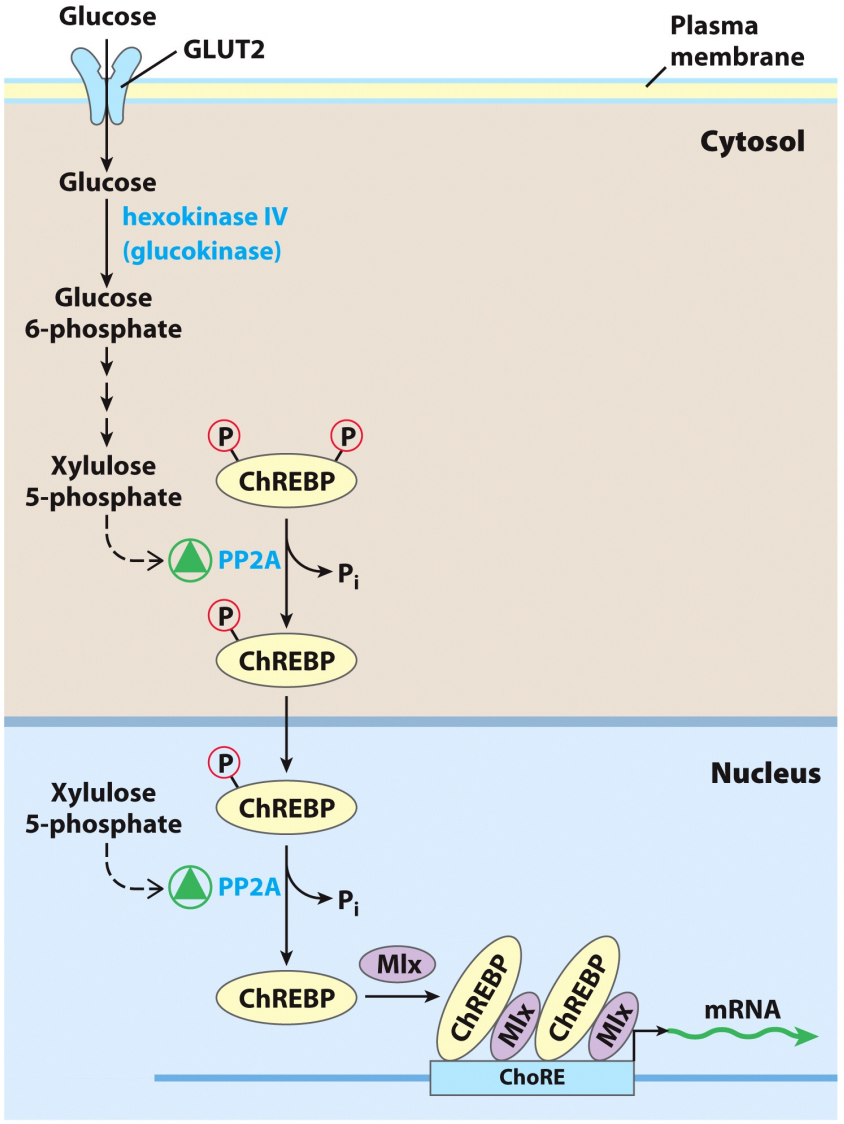


Figure 15-2
Lehninger Principles of Biochemistry, Sixth Edition

Lehninger, chapter 15

• Control of enzyme levels

- The concentrations of different enzymes vary widely in cellular extracts.
- Enzyme levels are controlled in large part by controlling the enzyme's rate of synthesis.
- Enzyme synthesis can often be induced or repressed by the presence or absence of certain metabolites.
- The rate of enzyme degradation can also be a factor in controlling enzyme levels.



Mechanism of activation of the transcription factor ChREBP (carbohydrate response element binding protein). In hepatocites it is phosphorylated and it cannot go into the nucleus. When the protein is dephosphorylated by PP2A, it can enter the nucleus, where it undergoes a second dephosphorylation and can bind to Mix. The complex ChREBP-Mix binds the carbohydrates response element (ChoRE) promoter and stimulates the transcription.

Figure 15-23
Lehninger Principles of Biochemistry, Sixth Edition

• Control of enzyme levels

- The concentrations of different enzymes vary widely in cellular extracts.
- Enzyme levels are controlled in large part by controlling the enzyme's rate of synthesis.
- Enzyme synthesis can often be induced or repressed by the presence or absence of certain metabolites.
- The rate of enzyme degradation can also be a factor in controlling enzyme levels.

TABLE 15–1 Average Half-Life of Proteins in Mammalian Tissues

Tissue	Average half-life (days)
Liver	0.9
Kidney	1.7
Heart	4.1
Brain	4.6
Muscle	10.7

Table 15-1
Lehninger Principles of Biochemistry, Sixth Edition

• Control of enzyme activity

- The catalytic activity of an enzyme can be controlled in three ways:

1. by substrates concentration (Michaelis-Menten kinetics).
Intracellular substrates concentration are often similar to K_m or lower (limiting factors).

2. by reversible interaction with ligands.
Low molecular weight ligands can interact with enzymes and exert allosteric effects. Frequently, the first or most important step in a metabolic pathway is under allosteric control in this way, enabling a cell to turn on or turn off an entire pathway easily and efficiently.

3. by covalent modification of the enzyme itself.
Covalent modifications include phosphorylations, ADP-ribosylation, and other, more complex alterations. Covalent modification often occurs as a result of action of regulatory cascades. Glycogen metabolism is regulated in this fashion. Enzymes that phosphorylate other enzymes are called protein kinases.

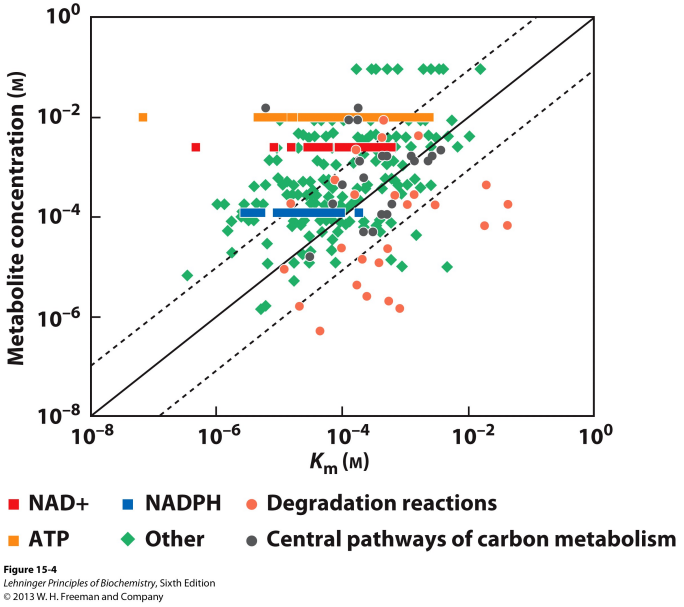


Figure 15-4
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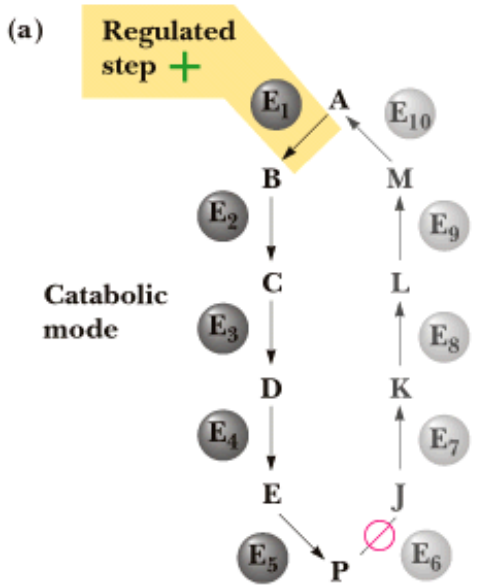
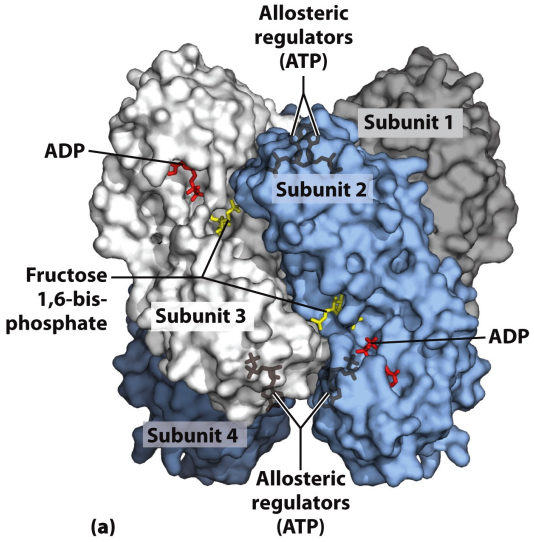
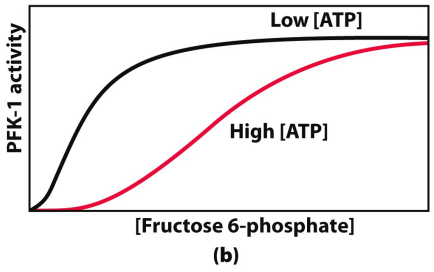


• Control of enzyme activity: allosteric regulation

- Typically associated with enzymes that catalyze irreversible reactions
- Allosteric regulators can cause feed back or feedforward regualtion
- Allosteric regulators are often related to the energy state of the cell
- This type of regulation allows for immediate response to changes in metabolic flux (milliseconds to seconds)
- Functions at local level



Regulation of phosphofructokinase-1 (PFK-1). In E. coli, the protein is composed by 4 subunits, each one with a catalytic site where fructose 1,6-biphosphate and ADP are in contact. There is a third allosteric regulatory site where ATP bind. s



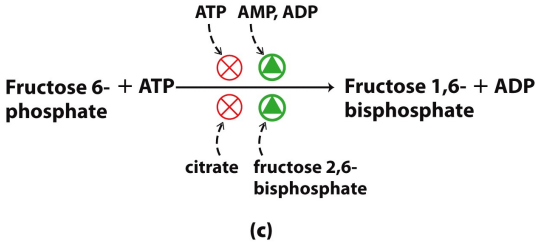


Figure 15-16
Lehninger Principles of Biochemistry, Sixth Edition

• Control of enzyme activity: covalent modification

- Covalent modification is usually the last step in signal transduction pathway
- Allows pathways to be rapidly up or down regulated by small amounts of triggering signal (HORMONES)
- Last longer than do allosteric regulation (seconds to minutes)
- Functions at whole body level

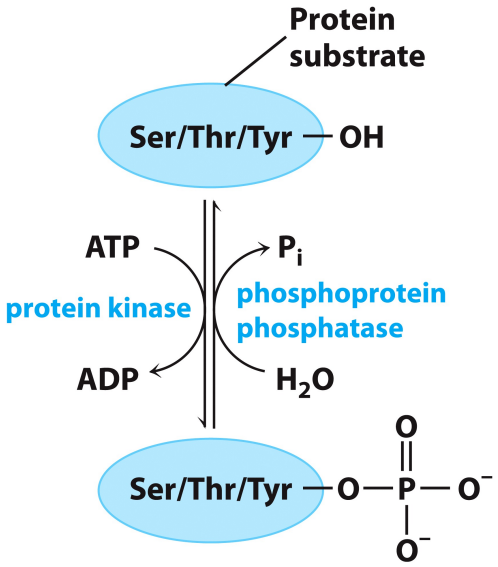


Figure 15-5
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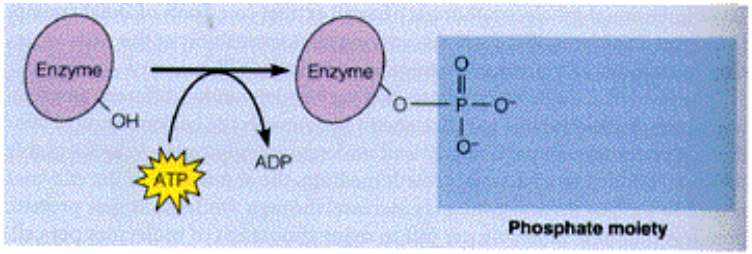
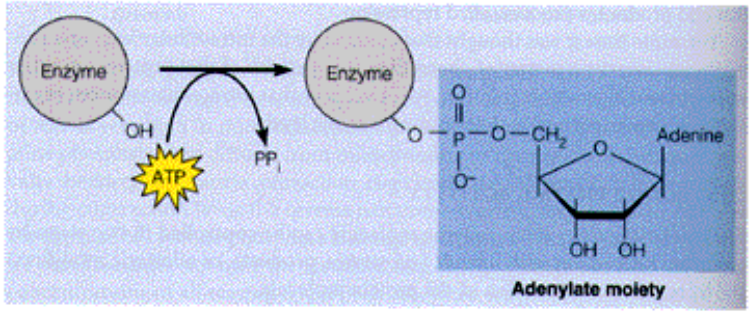
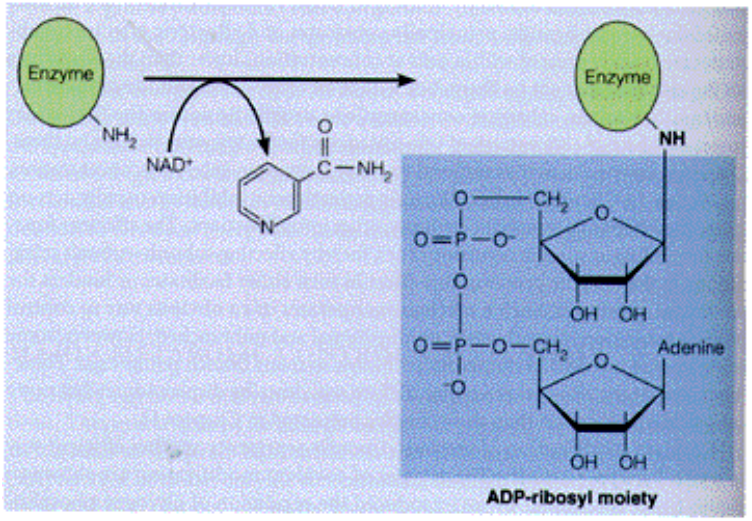


(a) Phosphorylation



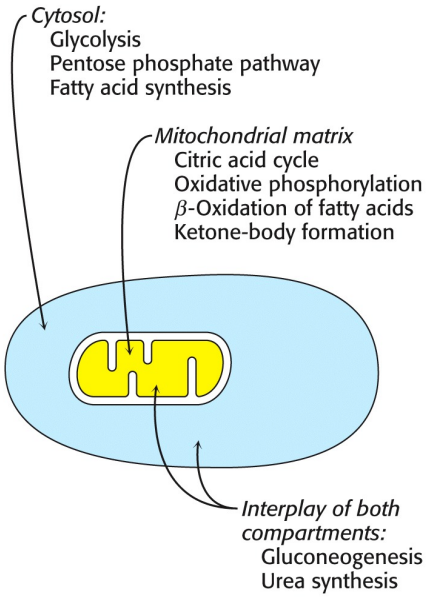
(b) Adenylylation

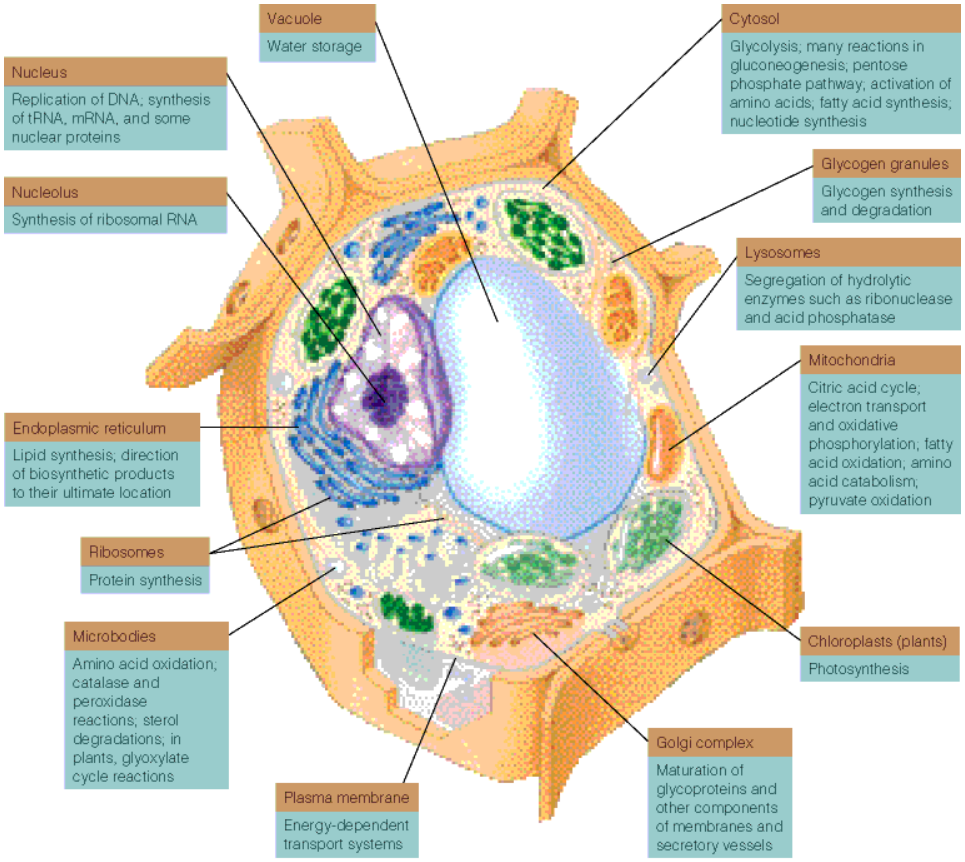


(c) ADP-ribosylation

• Compartmentation

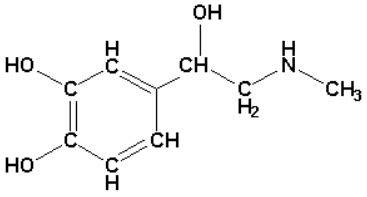
- Eukaryotic cells contain many different organelles and enzymes are distributed unevenly throughout them.
- For example, RNA polymerases are found in the nucleus and the nucleolus, where DNA transcription occurs.
- Enzymes of the citric acid cycle, on the other hand, are found in the mitochondria.
- Enzymes of fatty acid synthesis are found in the cytoplasm, but enzymes for fatty acid degradation are found in mitochondria.



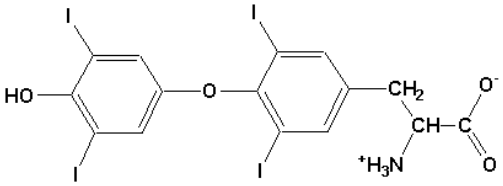


• Hormonal regulation

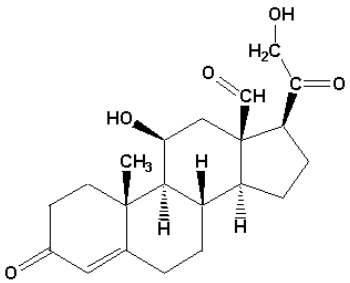
- Cells must respond to changes in the environment and/or to signals from other cells. The process of transmitting this information from outside of the cell to inside the cell is called signal transduction.
- The extracellular messengers that carry the information include hormones, growth factors, neurotransmitters, and pheromones.
- **Hormones** are substances synthesized in specialized cells and carried via the blood to remote target cells. There the hormones interact with specific receptors, resulting in specific metabolic changes in the target cell.



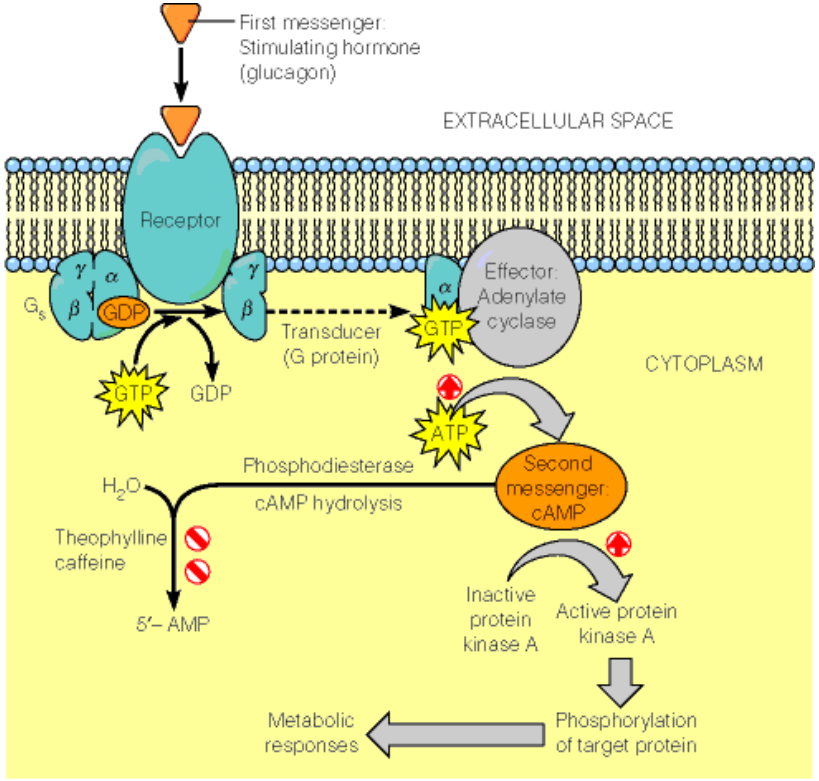
Epinephrine



Thyroxine



Aldosterone

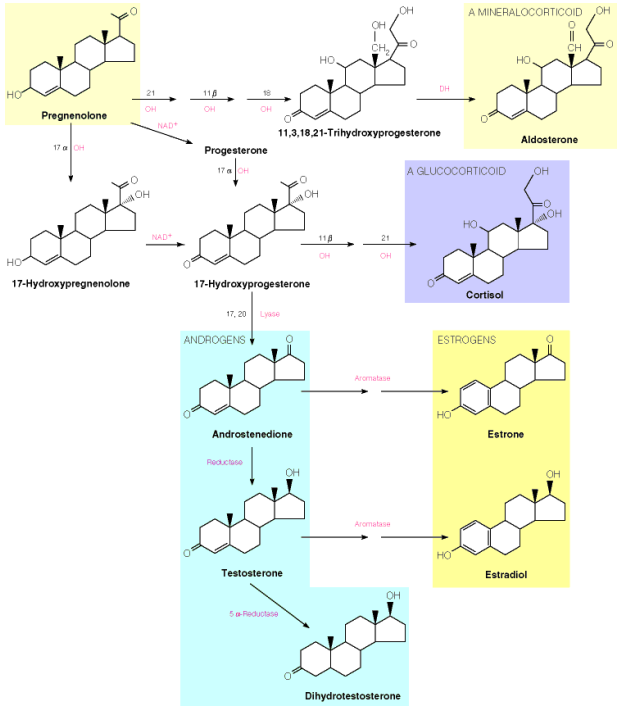


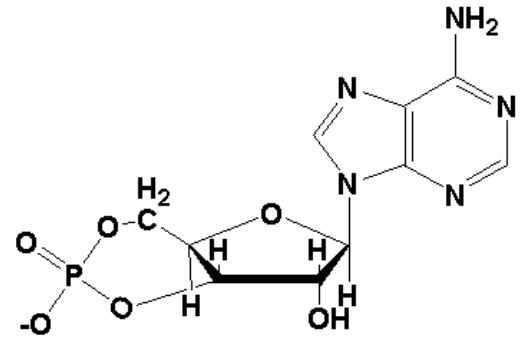
• Hormonal regulation

An example is the rapid generation of energy that results from secretion of adrenaline (epinephrine). The following two types of metabolic response to hormones are well understood:

1. Steroid hormones involve changes in gene expression.

2. Second messengers that control metabolic reactions are made in response to the binding of an extracellular substance (the first messenger). Common first messengers include glucagon and insulin. Common second messengers include cyclic AMP (or cAMP) and phosphoinositides.

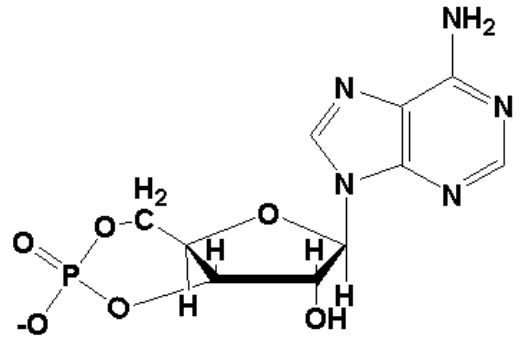




Cyclic adenosine monophosphate (cAMP)

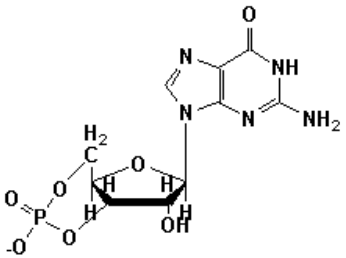
• Second messenger system

1. **Cyclic AMP** (**cAMP**) - Many signal transduction events involve the linked actions of a cell surface receptor, G protein, and adenylate cyclase. These events either stimulate or inhibit the synthesis of the second messenger, **cAMP**, inside the cell. Many intracellular processes are controlled, in turn, by the level of that second messenger. **cAMP** can affect transcription by binding to a protein called CREB (**cAMP** response element binding protein), and the resultant complex controls transcription of genes, including those encoding particular receptors.



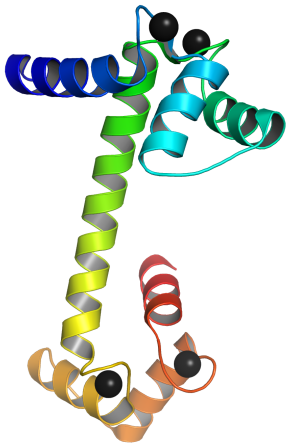
Cyclic adenosine monophosphate (cAMP)

2. **Cyclic GM**P **(cGM**P) - **Nitric oxid**e stimulates the synthesis of **cGM**P. Many cells contain a **cGMP**-stimulated protein kinase that, like the cAMP-activated enzyme, contains both catalytic and regulatory subunits.



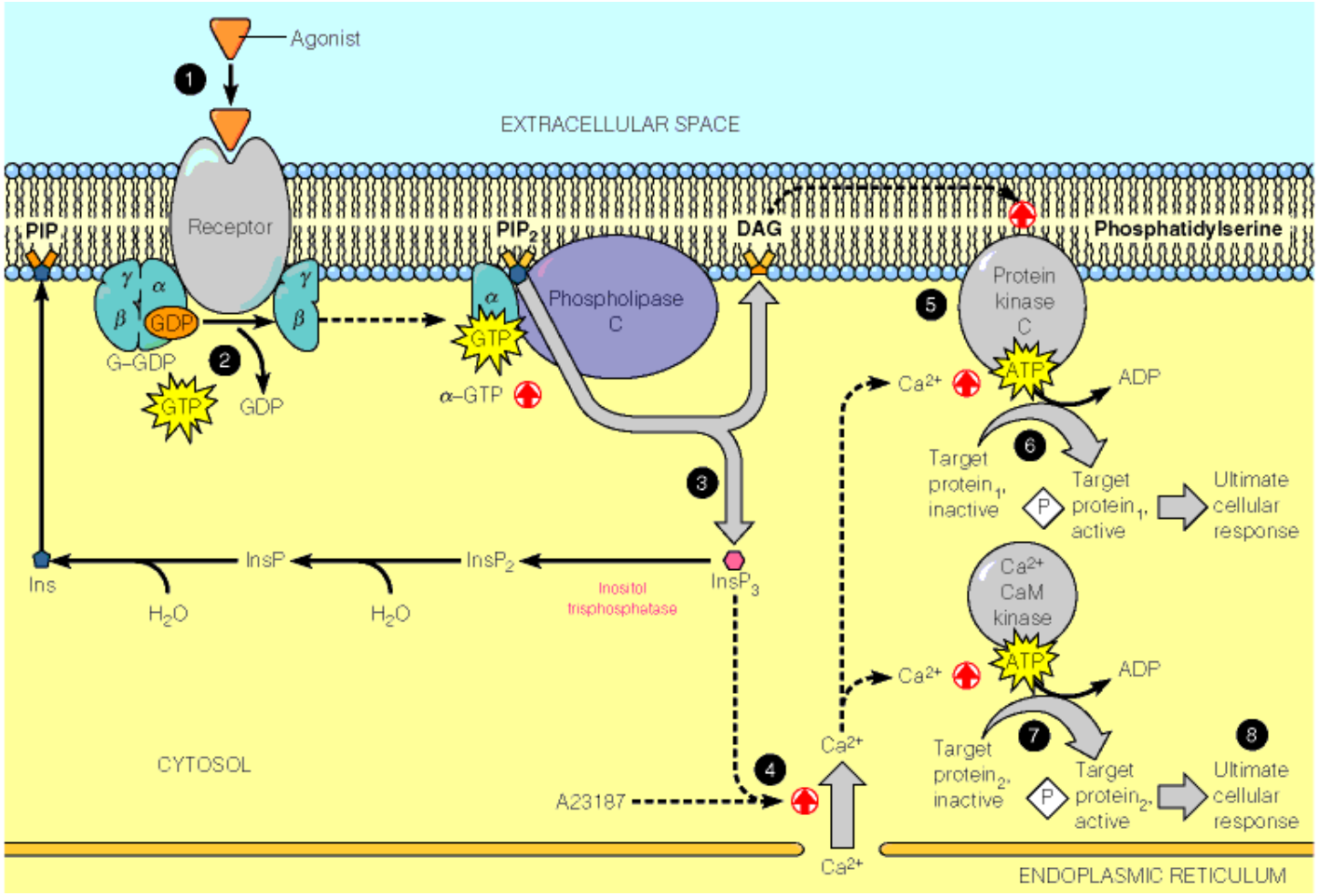
Cyclic guanosine monophosphate (cGMP)

3. **Calcium** - Calcium ion can be considered a second messenger. Many cells respond to extracellular stimuli by altering their intracellular calcium concentration, which in turn effects biochemical changes either by itself or through its interaction with calmodulin. Calcium levels themselves are controlled in large part by second messengers, including cAMP. Because cAMP regulates calcium influx, calcium ion may be more of a third messenger than a second messenger.



• Second messenger system

4. **Phosphoinositide/Diacylglycerol** - Cytosolic calcium ion levels also can be increased by release from intracellular calcium stores. Access to these intracellular stores is controlled by the phosphoinositide system. In the phosphoinositide system, hormonal stimulus activates a reaction that generates two second messengers. A specific lipid in the phosphoinositide family, phosphatidylinositol 4,5-bisphosphate (PIP_2), is a membrane-associated storage form for two second messengers.



• Distributive control of metabolism

- This concept recognizes that control of metabolic pathways is not simply a function of a single allosterically regulated enzyme in the pathway, but rather a function of all of the enzymes of a pathway.
- While enzymes catalyzing committed steps in pathways often play major roles in regulating the pathway, contributions can be made by all of the enzymes of the pathway.

• Specialization of organs

- Regulation in higher eukaryotes
- Organs have different metabolic roles i.e. Liver = gluconeogenesis, Muscle = glycolysis
- Metabolic specialization is the result of differential gene expression

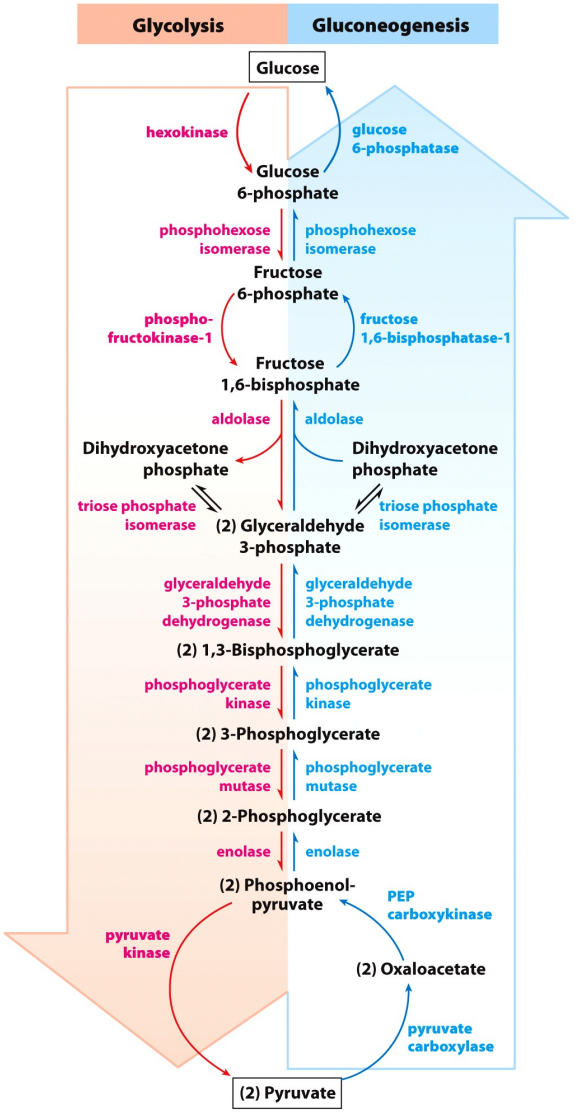


Figure 15-13
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