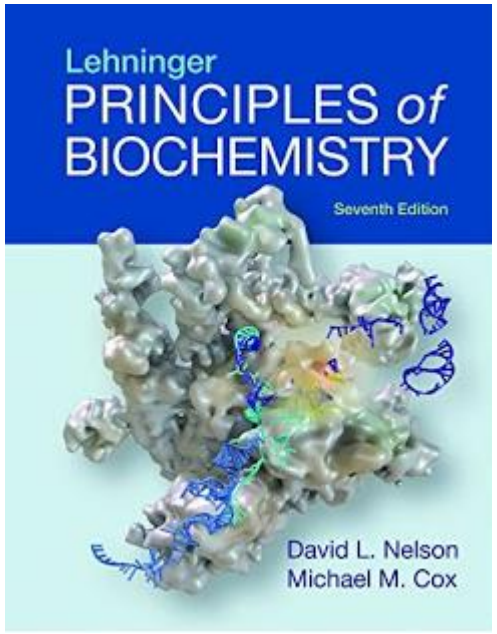
# Metabolism
# lecture 1

Dr. Bilal J M Aldahham

# References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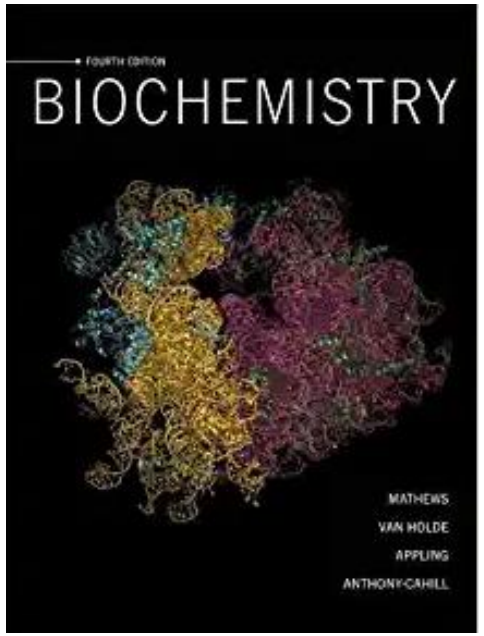
David L. Nelson
Michael M. Cox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MATHEWS
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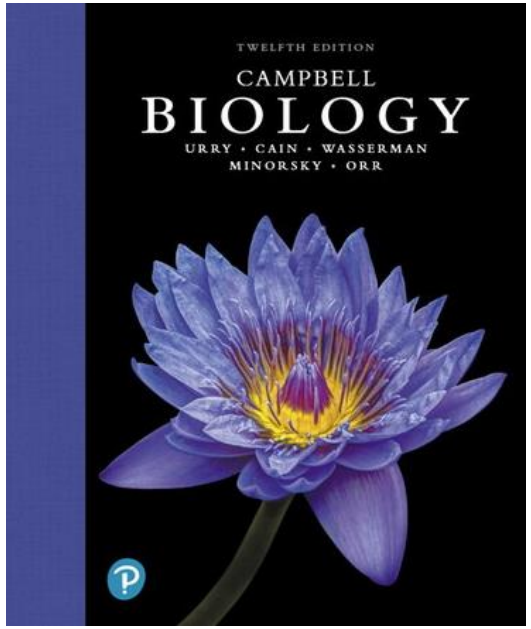
ANTHONY-CAHILL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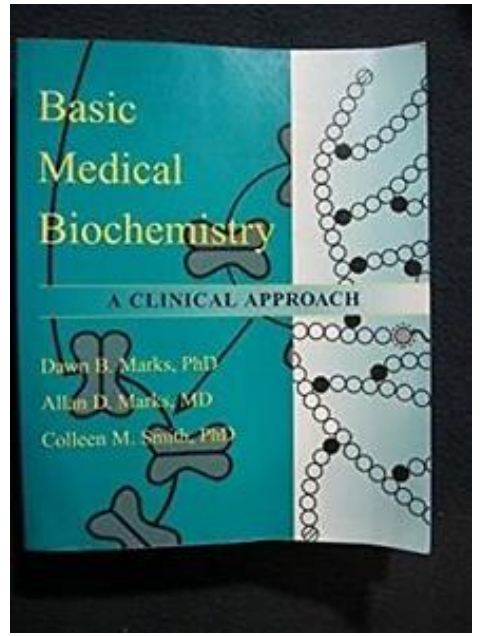

Basic
Medical
Biochemistry
A CLINICAL APPROACH
Dawn B. Marks, PhD
Allan D. Marks, MD
Colleen M. Smith, PhD

# Requirements

- Two exams (15 +15)
- Discussion & Home works  (10)

- Final 60
- No practical part

# Description

- The teaching should provide knowledge of the body uptake of nutrients and these storing and renewal in different physiological conditions. The student should be able to integrate the received knowledge so that she/he within this field can explain the background of relevant diseases

# Course outcomes

- After completing the course, students should be able to:

- discuss basic concepts and terminology of metabolism and bioenergetics
- describe the regulation of metabolic pathways
- compare and contrast glycolysis and gluconeogenesis
- diagram and describe the citric acid cycle
- describe the regulation of mammalian metabolism through hormones

# Syllabus

- Introduction to metabolism and bioenergetics
- Carbohydrates metabolism
- Lipids metabolism
- Proteins metabolism
- Nutrition and metabolism
- Hormones managing
- Metabolic diseases

# General Overview

- Metabolism is a highly coordinated cellular activity in which many multienzyme systems (metabolic pathways) cooperate to

1. obtain chemical energy by capturing solar energy or degrading energy-rich nutrients from the environment
2. convert nutrient molecules into the cell's own characteristic molecules, including precursors of macromolecules
3. polymerize monomeric precursors into macromolecules: proteins, nucleic acids, and polysaccharides
4. synthesize and degrade biomolecules required for specialized cellular functions, such as membrane lipids, intracellular messengers, and pigments.

# Definitions

## An organism's metabolism transforms matter and energy, subject to the laws of thermodynamics

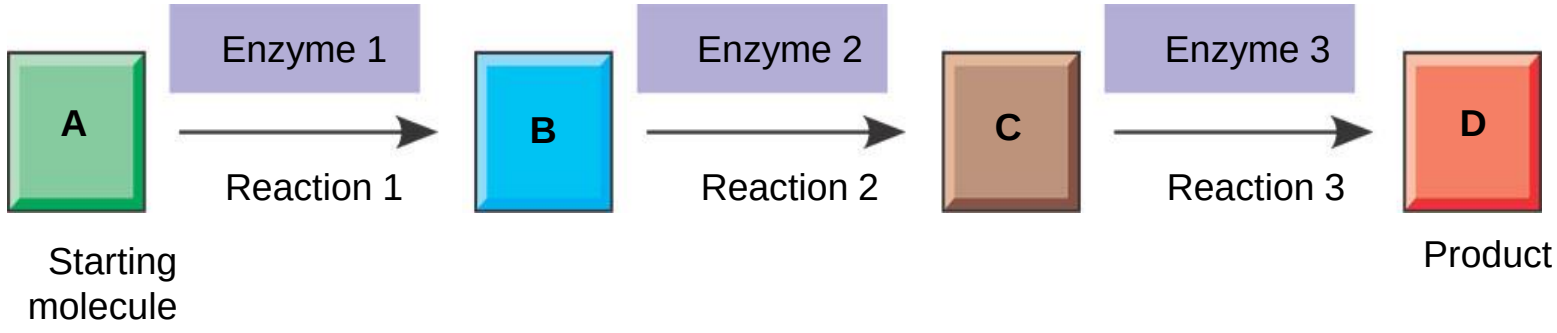
- **Metabolism** is the totality of an organism's chemical reactions
- Metabolism is an emergent property of life that arises from interactions between molecules within the cell

## Organization of the Chemistry of Life into Metabolic Pathways

- A **metabolic pathway** begins with a specific molecule and ends with a product
- Each step is catalyzed by a specific enzyme

# Organization of the Chemistry of Life into Metabolic Pathways

- A metabolic pathway has many steps
  - That begin with a specific molecule and end with a product
  - That are each catalyzed by a specific enzyme

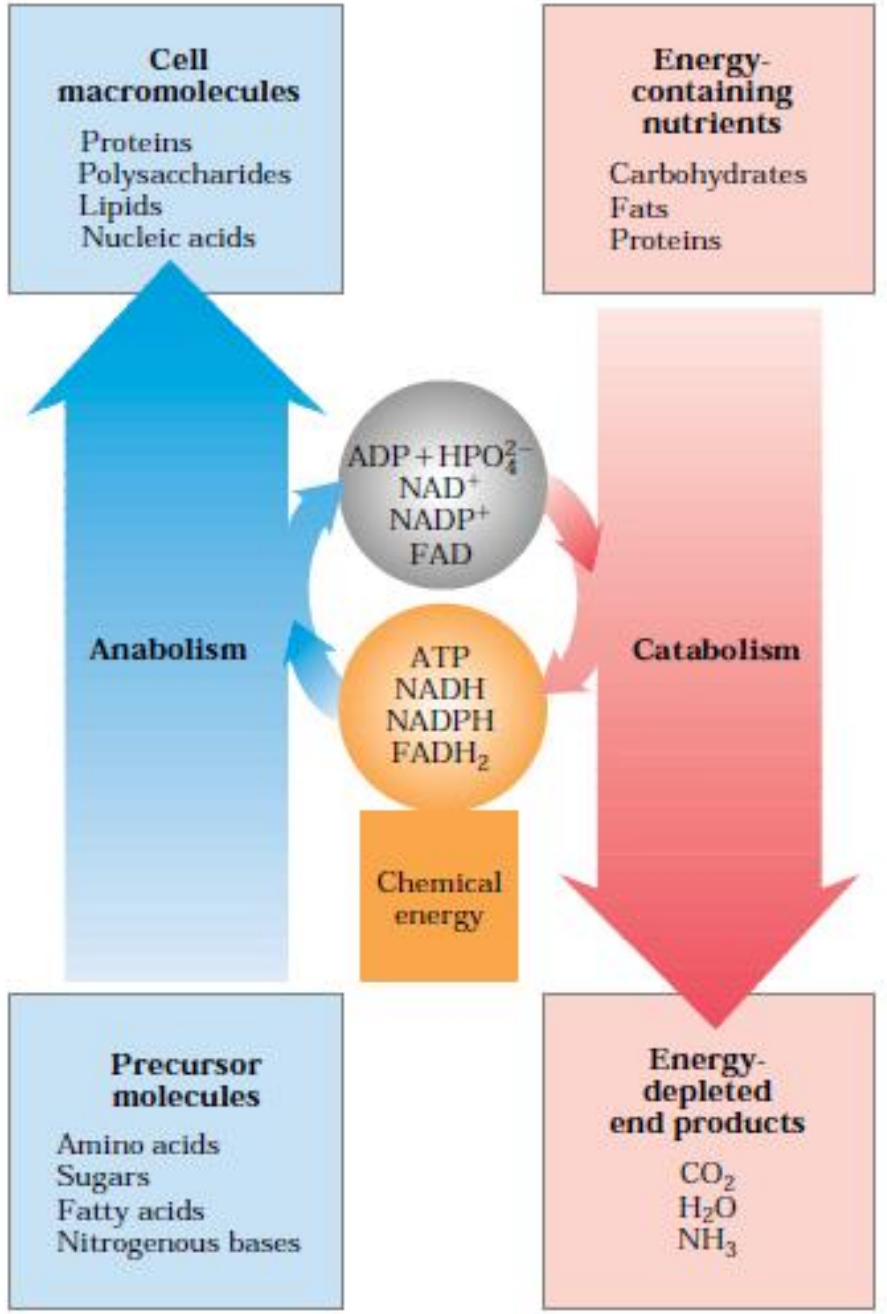


# Definitions

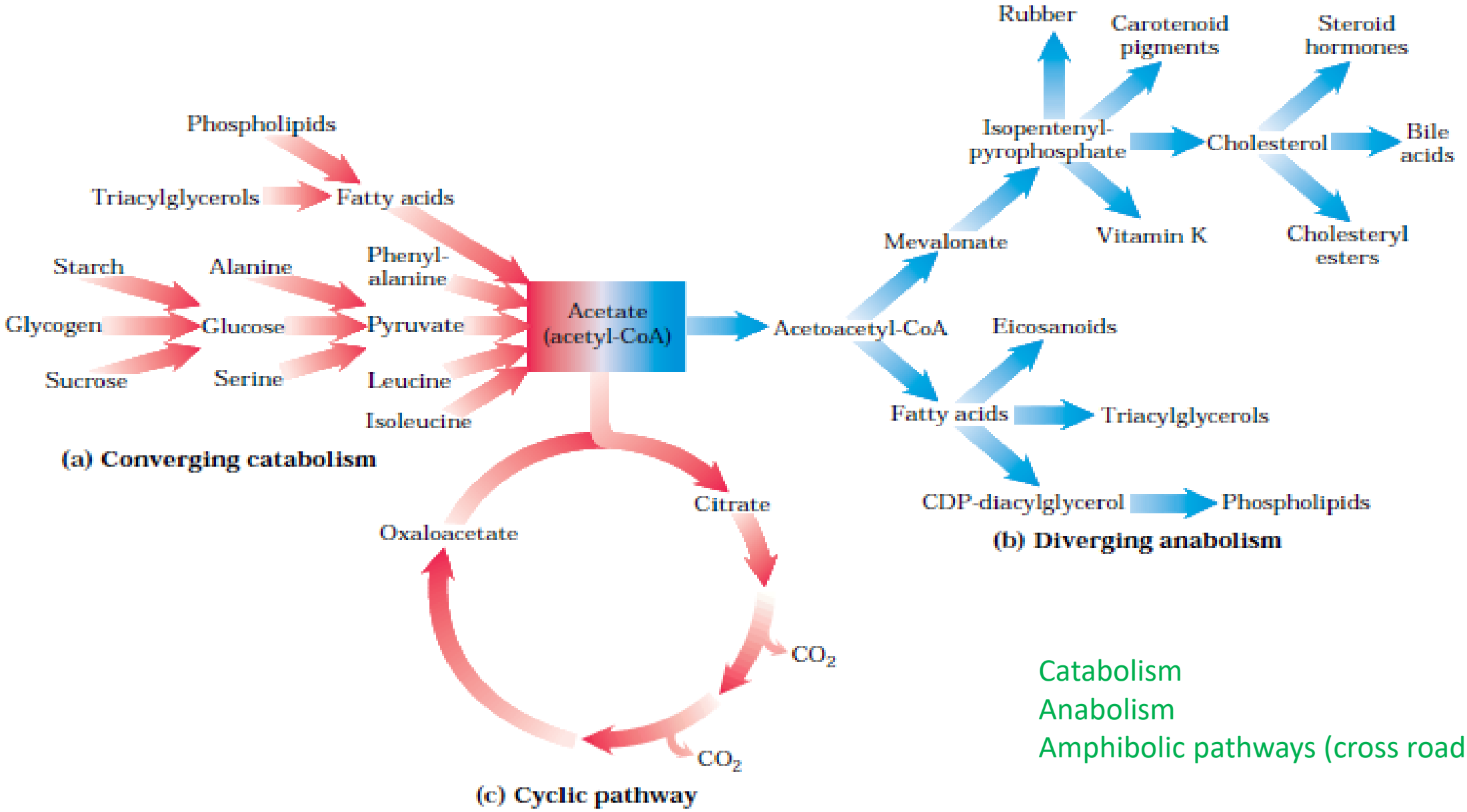
- **Catabolic pathways** release energy by breaking down complex molecules into simpler compounds
- Cellular respiration, the breakdown of glucose in the presence of oxygen, is an example of a pathway of catabolism

- **Anabolic pathways** consume energy to build complex molecules from simpler ones
- The synthesis of protein from amino acids is an example of anabolism

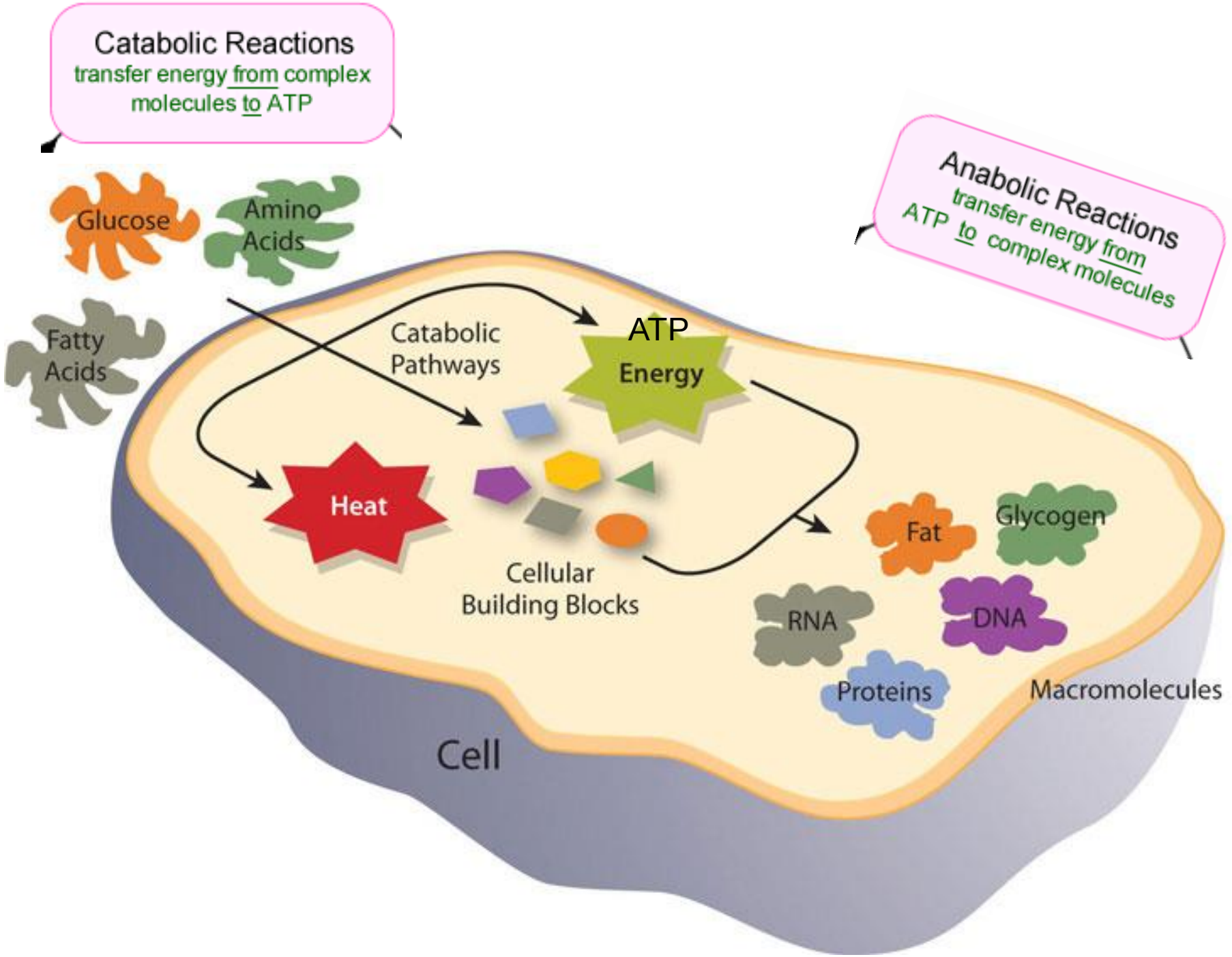
# Energy relationships between catabolic and anabolic pathways



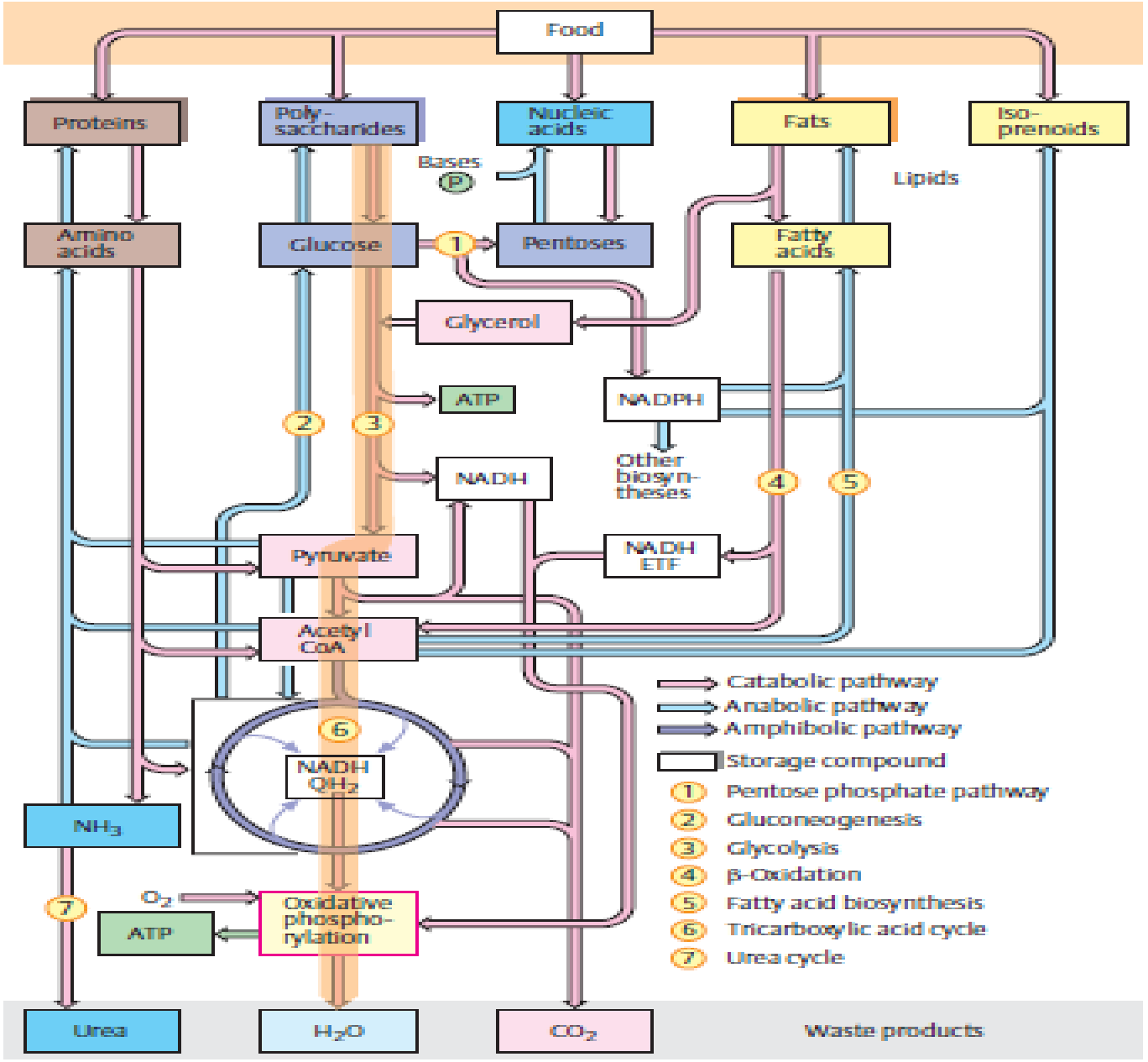
# Three types of nonlinear metabolic pathways



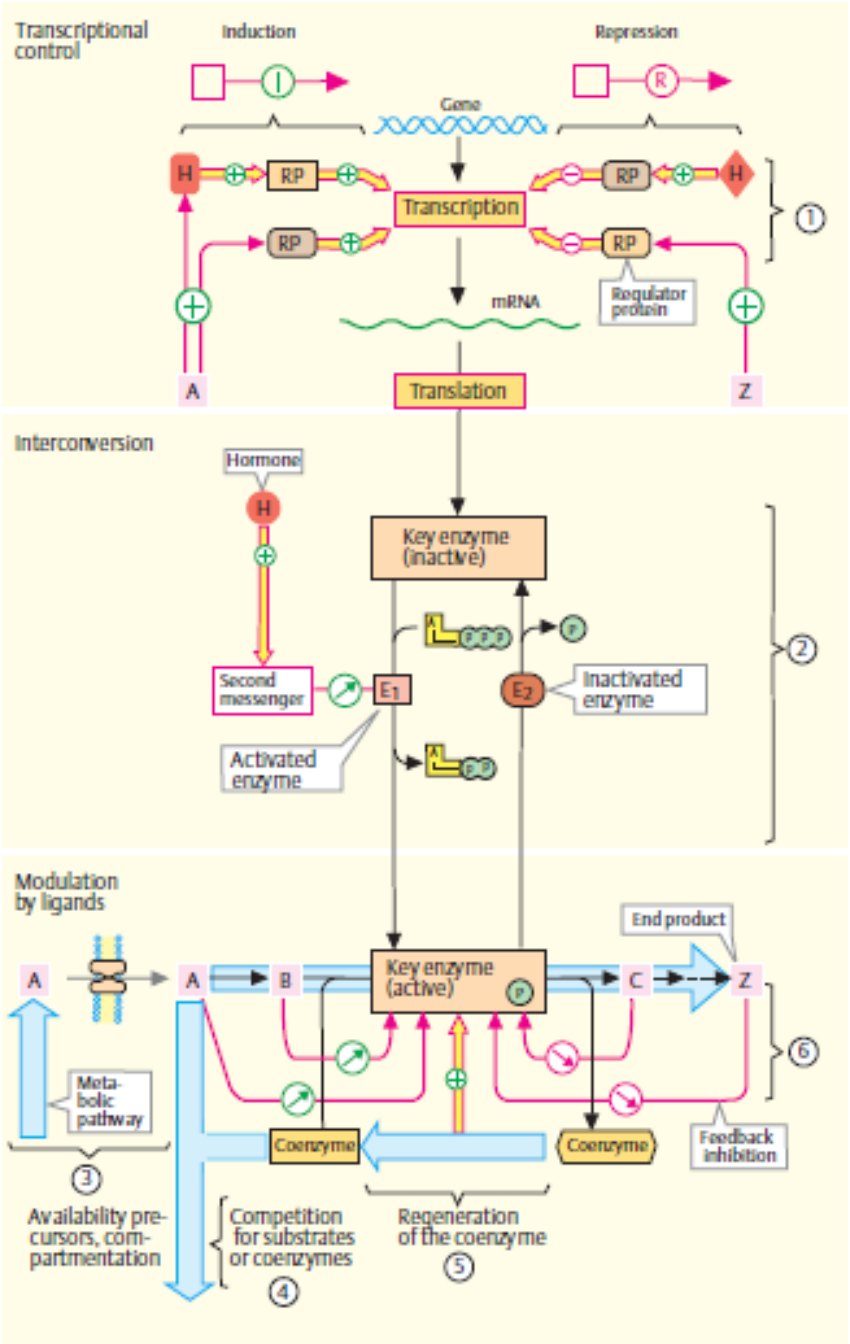

Catabolism
Anabolism
Amphibolic pathways (cross road)


Catabolic Reactions
transfer energy from complex molecules to ATP
Anabolic Reactions
transfer energy from ATP to complex molecules
Glucose
Amino Acids
Fatty Acids
Catabolic Pathways
ATP
Energy
Heat
Cellular Building Blocks
Fat
Glycogen
RNA
DNA
Proteins
Macromolecules
Cell

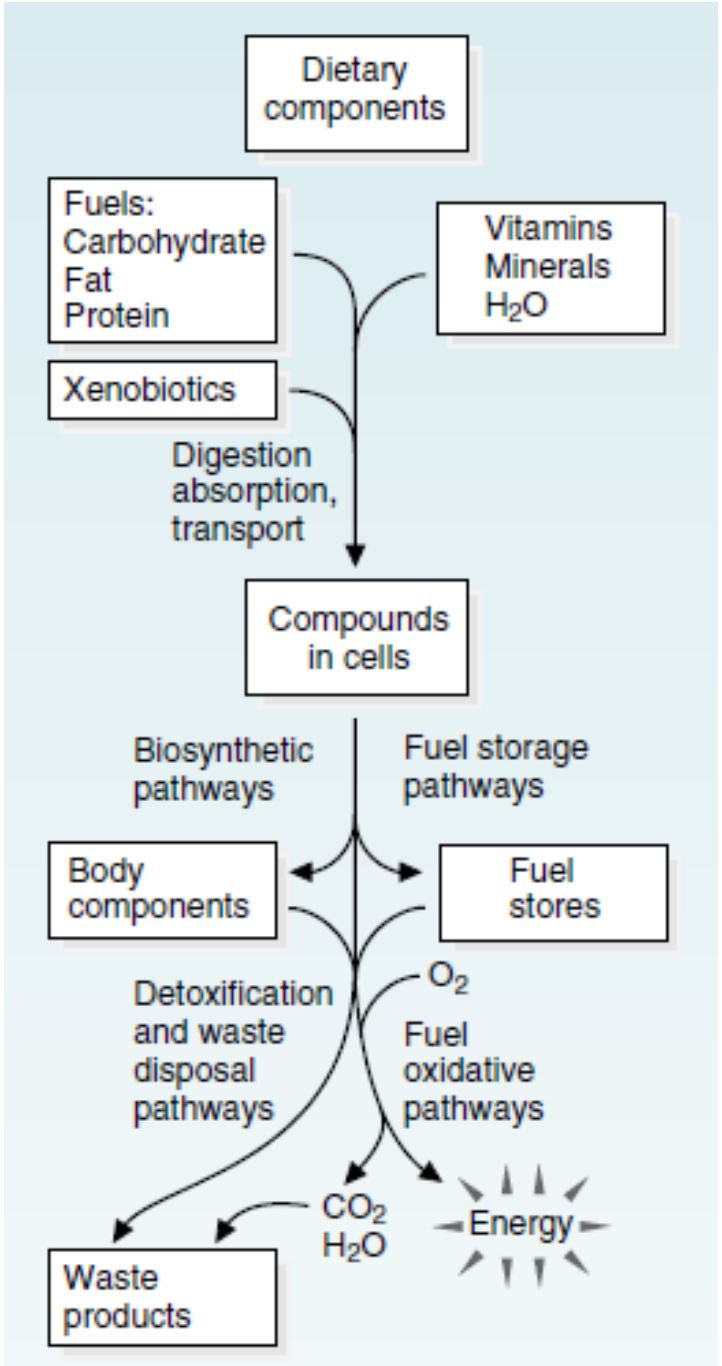
# Intermediary metabolism: overview



# Fundamental mechanisms of regulation



# General metabolic routes for dietary components in the body



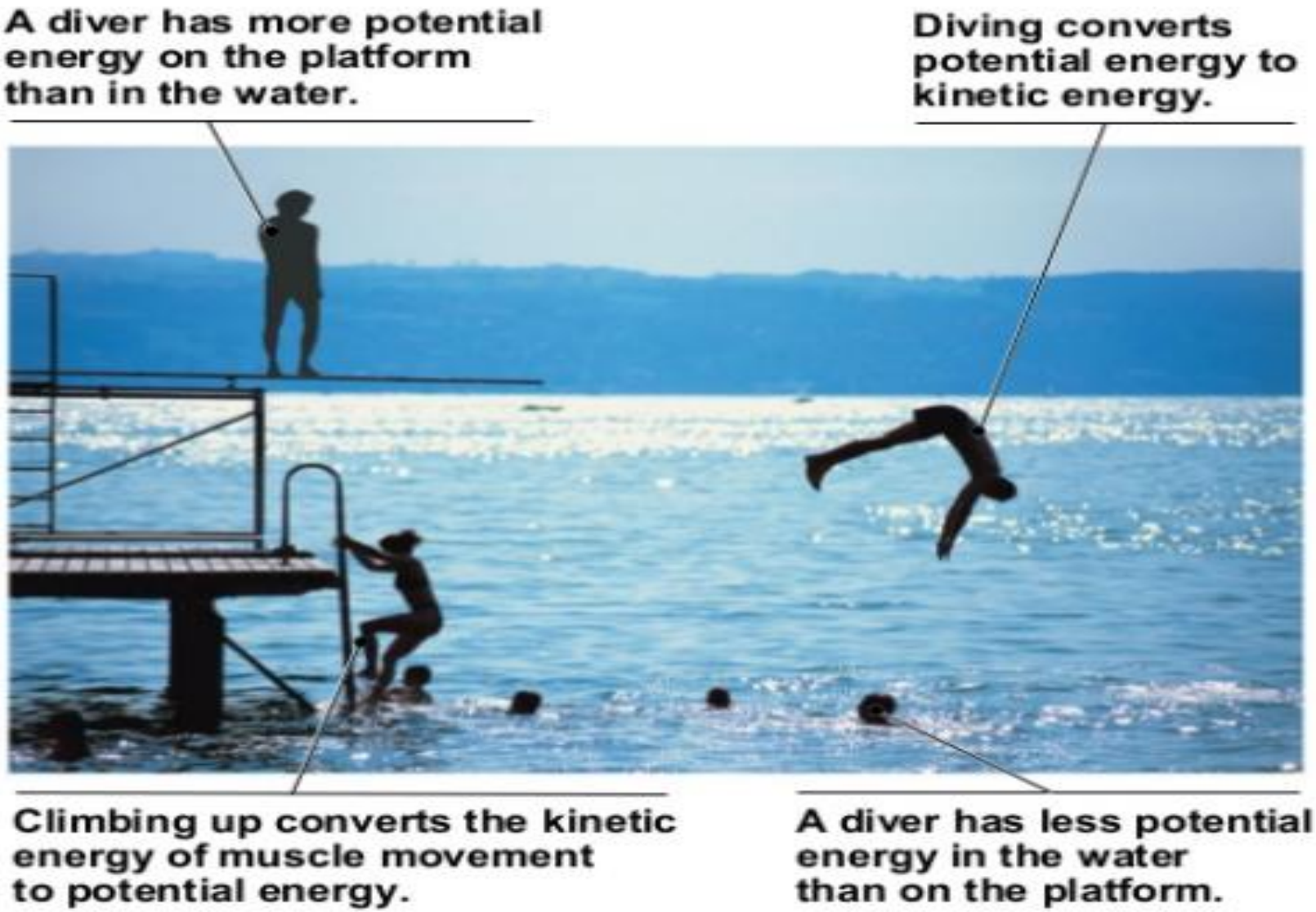
# Bioenergetics

- **Bioenergetics** is the study of how organisms manage their energy resources

- **Energy** is the capacity to cause change
- Energy exists in various forms, some of which can perform work

- **Kinetic energy** is energy associated with motion
- **Heat (thermal energy)** is kinetic energy associated with random movement of atoms or molecules
- **Potential energy** is energy that matter possesses because of its location or structure
- **Chemical energy** is potential energy available for release in a chemical reaction
- Energy can be converted from one form to another

# Convert Energy



# Bioenergetics and Thermodynamics

## *The First Law of Thermodynamics*

- According to the **first law of thermodynamics**, the energy of the universe is constant
  - *Energy can be transferred and transformed, but it cannot be created or destroyed*
- The first law is also called the principle of conservation of energy

# Bioenergetics and Thermodynamics

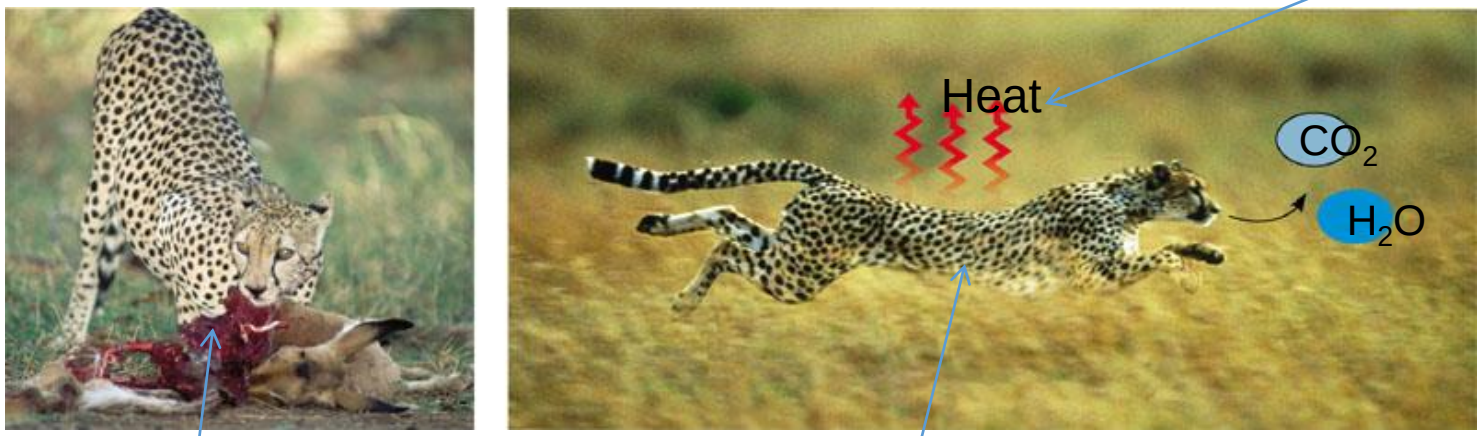
## *The Second Law of Thermodynamics*

- During every energy transfer or transformation, some energy is unusable, and is often lost as heat
- According to the **second law of thermodynamics**
  - *Every energy transfer or transformation increases the **entropy** (disorder) of the universe*

# LAWS OF THERMODYNAMICS

Is the study of energy transformations

Most energy is lost as heat




Chemical potential energy TO Kinetic energy

**1st Law:** Energy can be transferred and transformed but it can't be created or destroyed.

**2nd Law:** Every energy transfer or transformation increases the entropy of the universe.

$$\Delta G = \Delta H - T\Delta S$$

**Gibbs free energy, *G*,** expresses the amount of energy capable of doing work during a reaction at constant temperature and pressure. When a reaction proceeds with the release of free energy (that is, when the system changes so as to possess less free energy), the free-energy change, $\Delta G$, has a negative value and the reaction is said to be exergonic. In endergonic reactions, the system gains free energy and $\Delta G$ is positive.

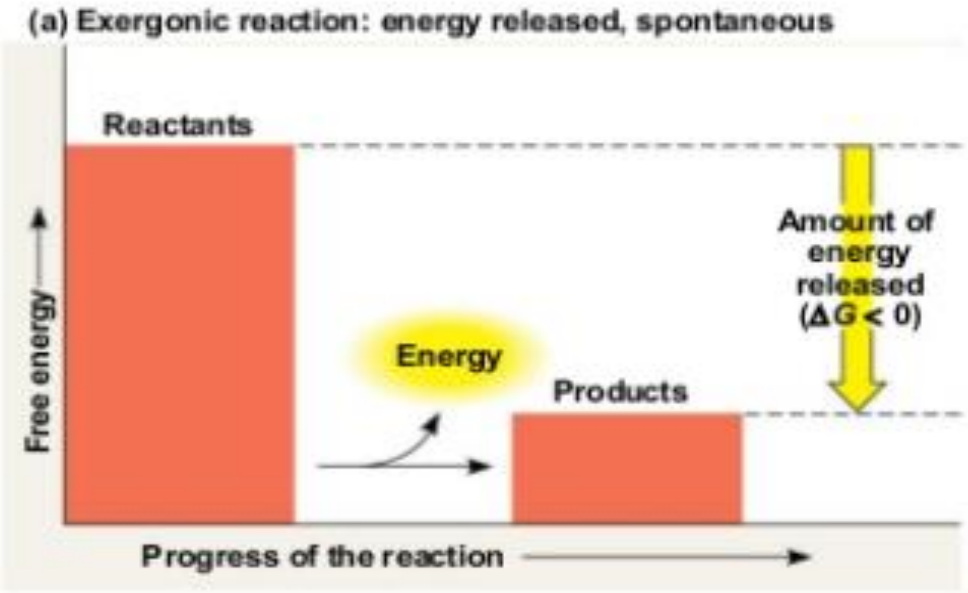
**Enthalpy, *H*,** is the heat content of the reacting system. It reflects the number and kinds of chemical bonds in the reactants and products. When a chemical reaction releases heat, it is said to be exothermic; the heat content of the products is less than that of the reactants and $\Delta H$ has, by convention, a negative value. Reacting systems that take up heat from their surroundings are endothermic and have positive values of $\Delta H$.

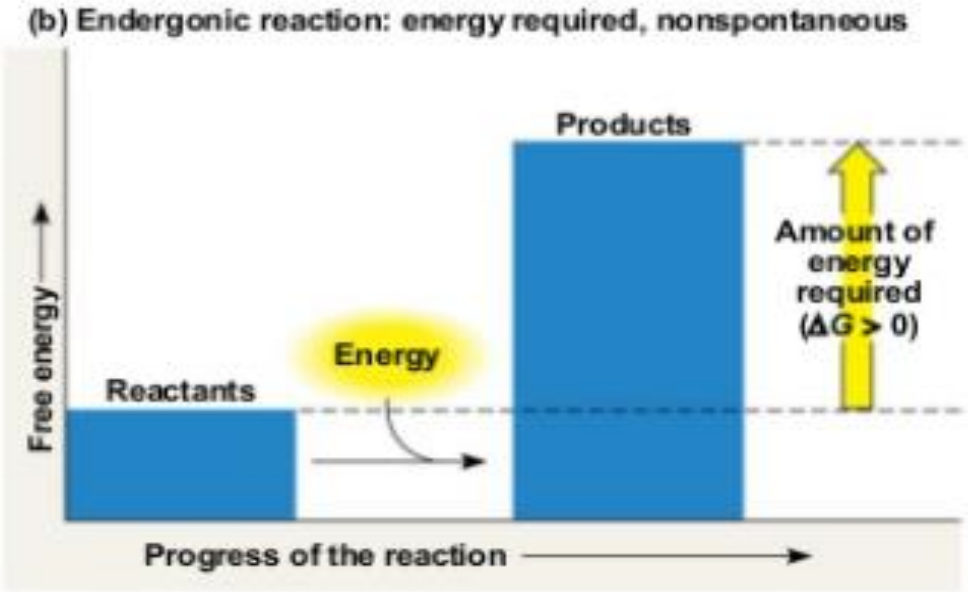
**Entropy, *S*,** is a quantitative expression for the randomness or disorder in a system (see Box 1–3). When the products of a reaction are less complex and more disordered than the reactants, the reaction is said to proceed with a gain in entropy.

# Exergonic &Endergonic

***Exergonic and Endergonic Reactions in Metabolism***

- An **exergonic reaction** proceeds with a net release of free energy and is spontaneous
- An **endergonic reaction** absorbs free energy from its surroundings and is nonspontaneous



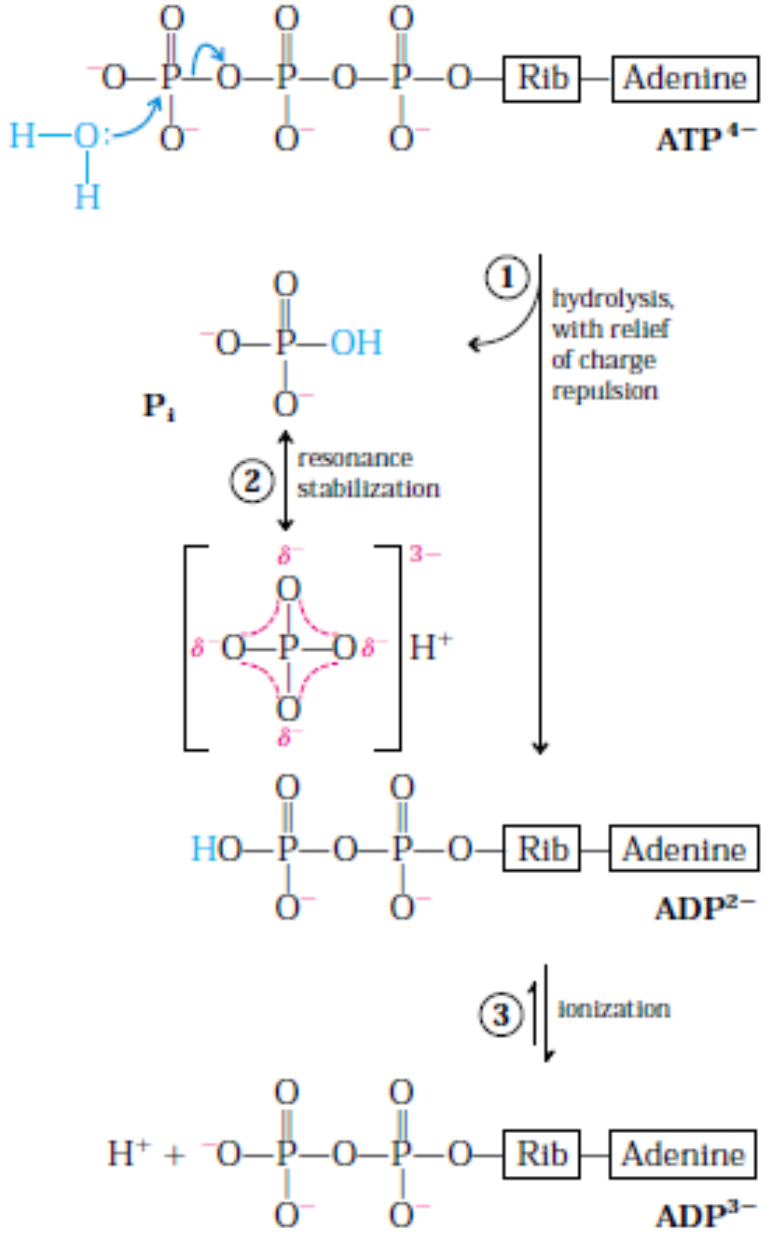



# Currency of Energy

**ATP powers cellular work by coupling exergonic reactions to endergonic reactions**

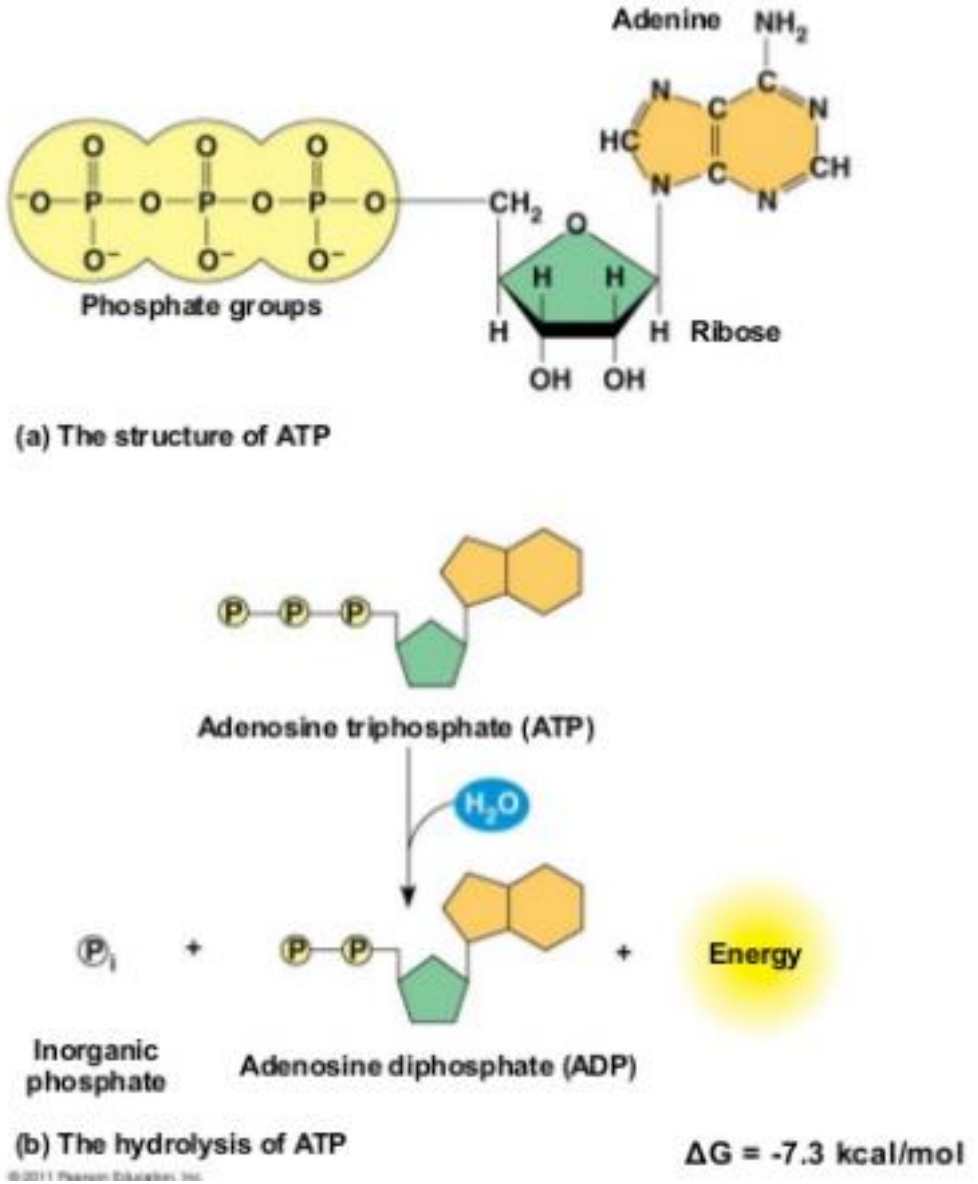
- A cell does three main kinds of work
  - Chemical
  - Transport
  - Mechanical
- To do work, cells manage energy resources by **energy coupling**, the use of an exergonic process to drive an endergonic one
- Most energy coupling in cells is mediated by ATP

# Phosphoryl Group Transfers and ATP




$$ATP^{4-} + H_2O \longrightarrow ADP^{3-} + P_i^{2-} + H^+$$
$$\Delta G'^{\circ} = -30.5 \text{ kJ/mol}$$

1 cal = 4.18 J

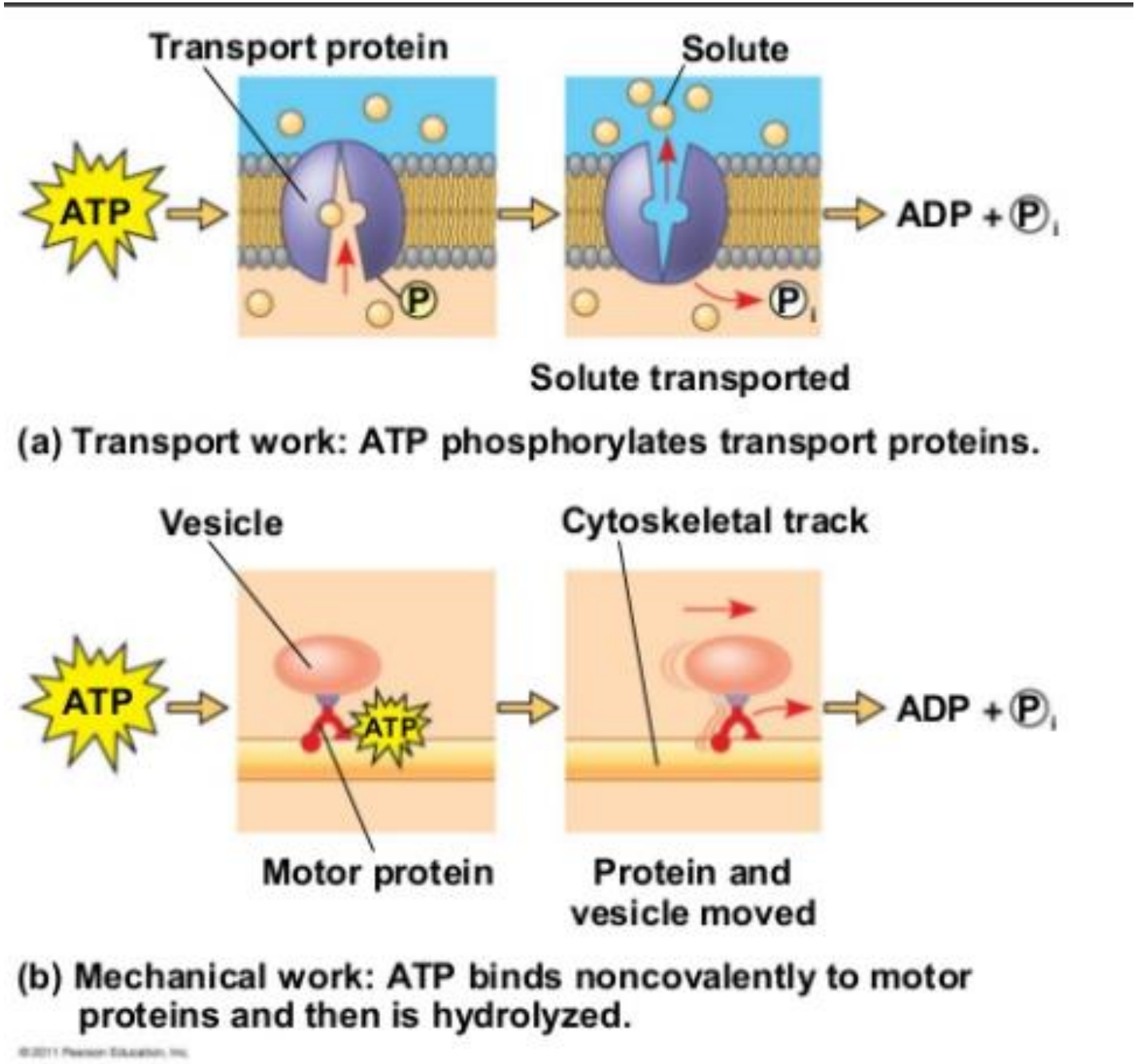

Adenine
Phosphate groups
Ribose
(a) The structure of ATP
Adenosine triphosphate (ATP)
Energy
Inorganic phosphate
Adenosine diphosphate (ADP)
(b) The hydrolysis of ATP
ΔG = -7.3 kcal/mol

# How the Hydrolysis of ATP Performs Work

- The three types of cellular work (mechanical, transport, and chemical) are powered by the hydrolysis of ATP
- In the cell, the energy from the exergonic reaction of ATP hydrolysis can be used to drive an endergonic reaction
- Overall, the coupled reactions are exergonic

- ATP drives endergonic reactions by phosphorylation, transferring a phosphate group to some other molecule, such as a reactant
- The recipient molecule is now called a **phosphorylated intermediate**

# Types of energy consuming



# The Regeneration of ATP

- ATP is a renewable resource that is regenerated by addition of a phosphate group to adenosine diphosphate (ADP)
- The energy to phosphorylate ADP comes from catabolic reactions in the cell
- The ATP cycle is a revolving door through which energy passes during its transfer from catabolic to anabolic pathways

# The Regeneration of ATP

- Catabolic pathways

Drive the regeneration of ATP from ADP and – phosphate

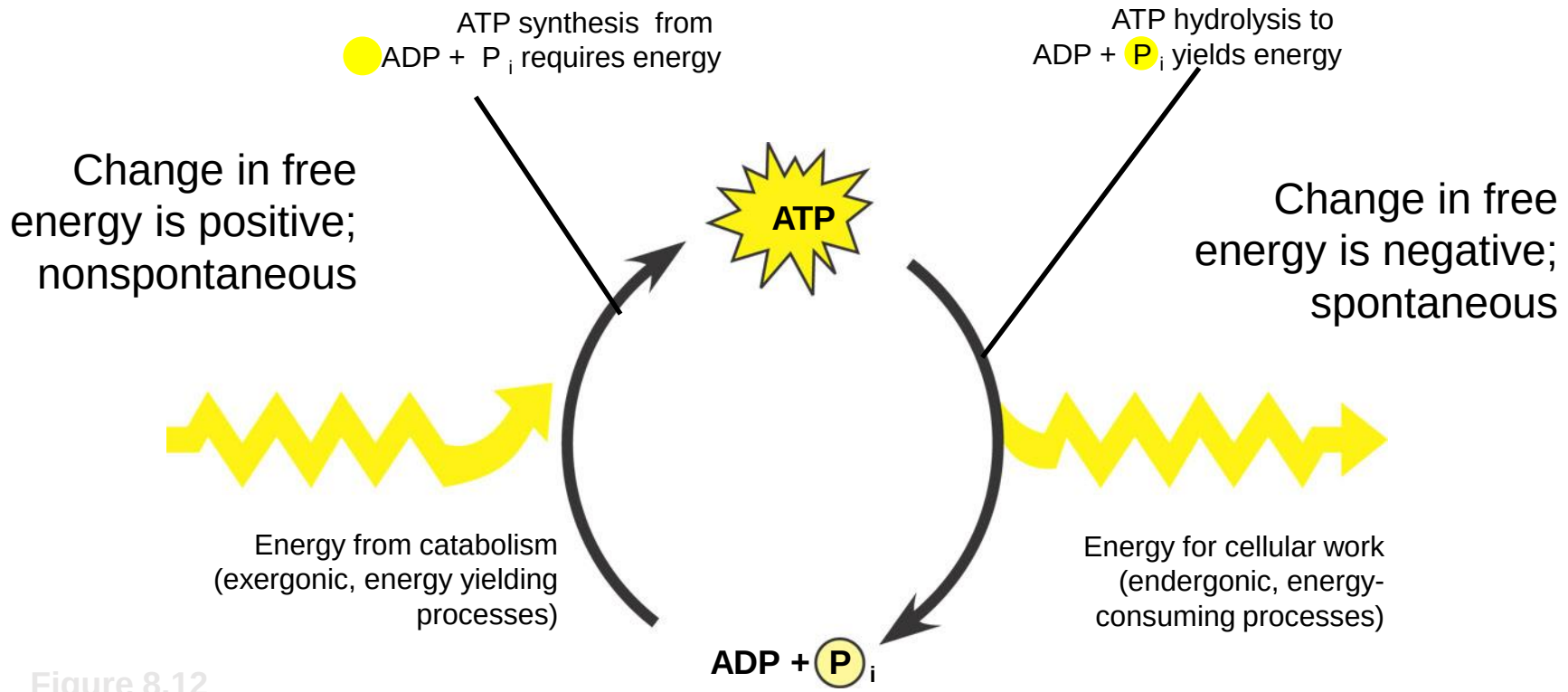



Figure 8.12

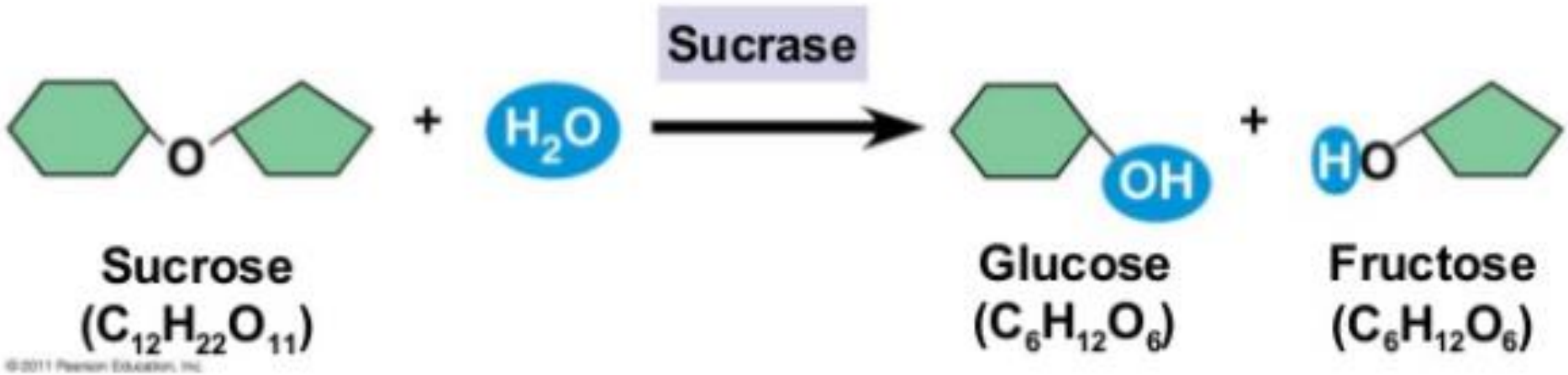
# Metabolism
# lecture 2 Enzymes

Dr. Bilal J M Aldahham

## Enzymes speed up metabolic reactions by lowering energy barriers

- A **catalyst** is a chemical agent that speeds up a reaction without being consumed by the reaction
- An **enzyme** is a catalytic protein
- Hydrolysis of sucrose by the enzyme sucrase is an example of an enzyme-catalyzed reaction

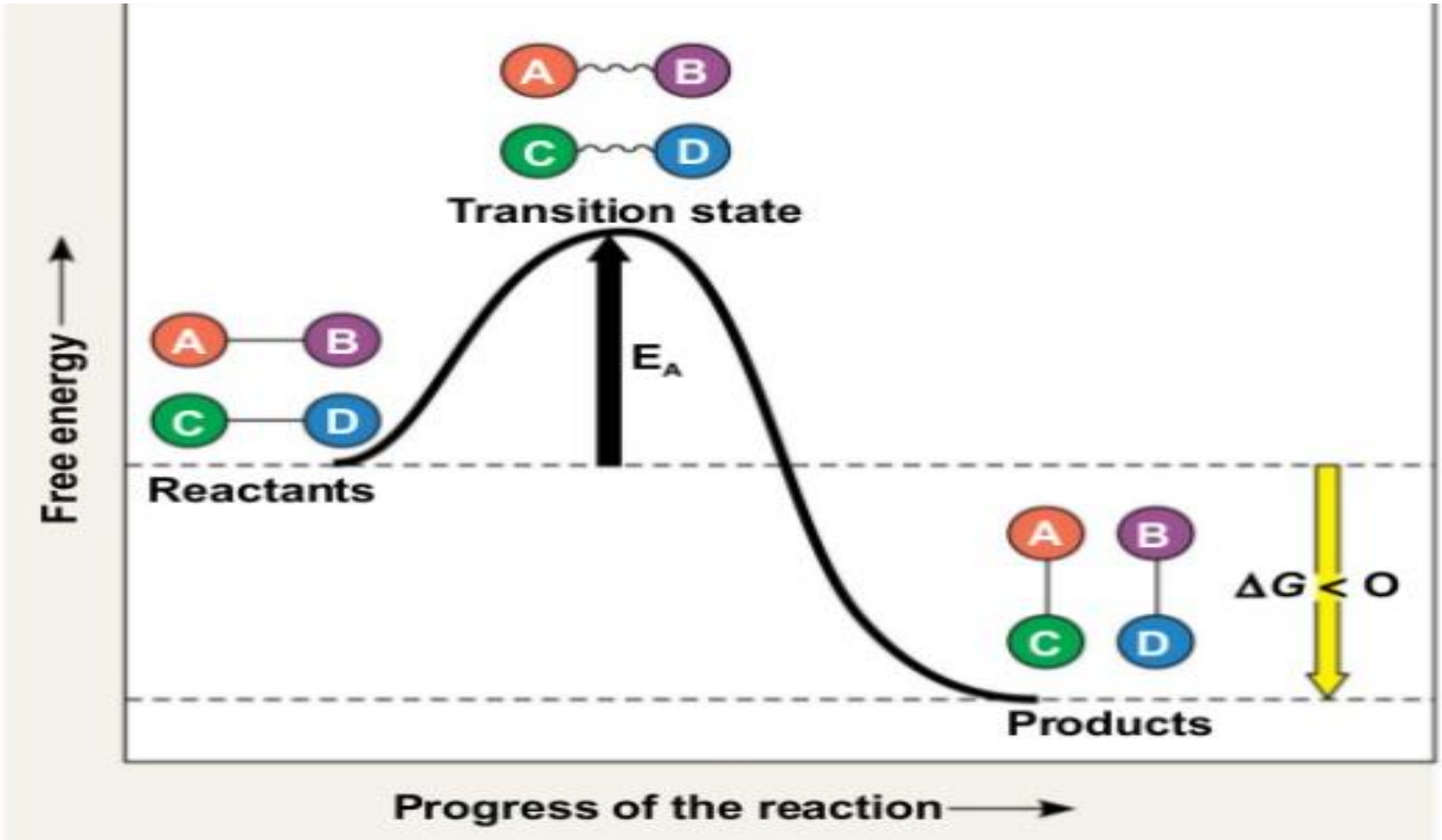
# Example


Sucrase
O
+
$H_2O$
OH
+
HO
Sucrose
($C_{12}H_{22}O_{11}$)
Glucose
($C_6H_{12}O_6$)
Fructose
($C_6H_{12}O_6$)

# The Activation Energy Barrier

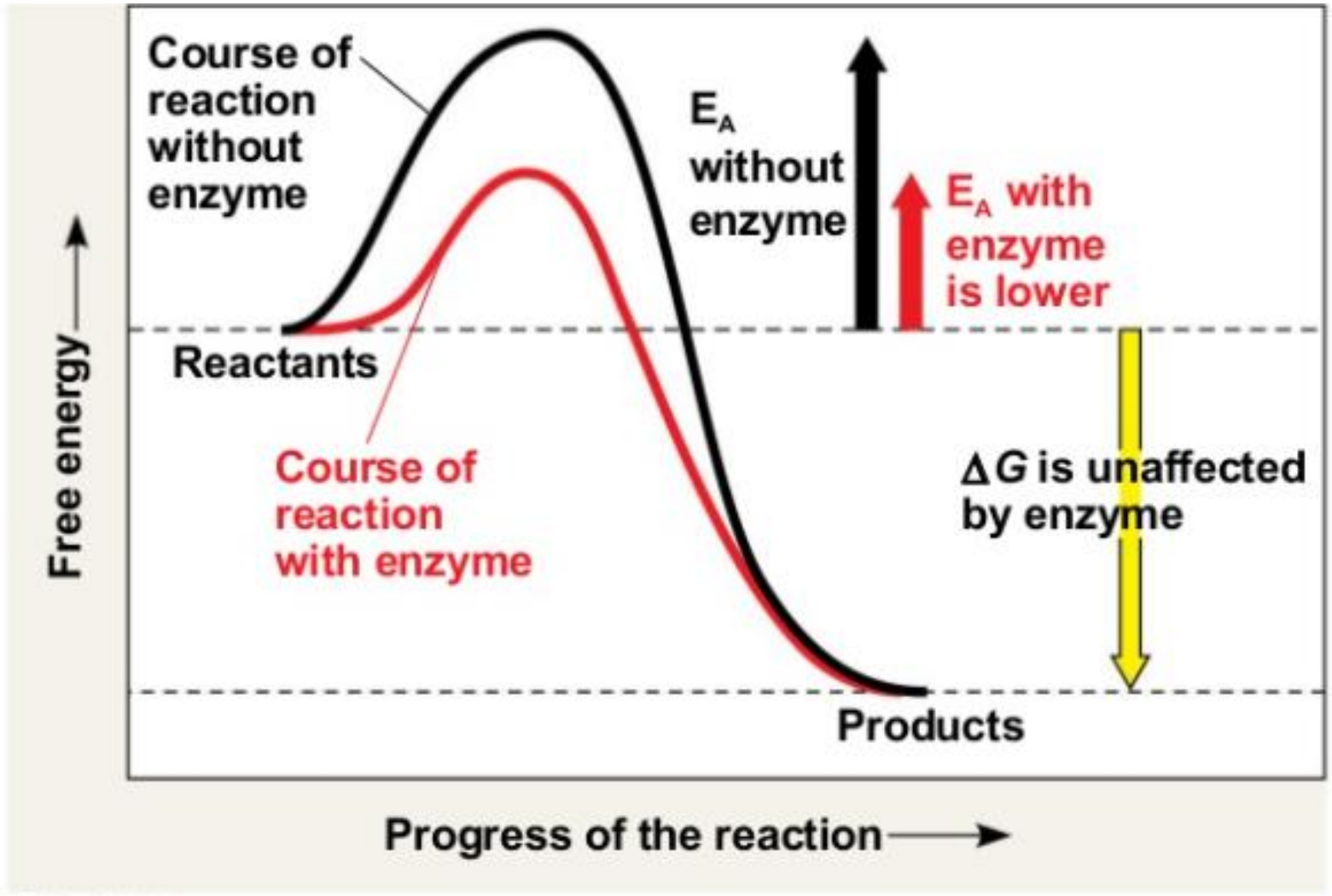
- Every chemical reaction between molecules involves bond breaking and bond forming
- The initial energy needed to start a chemical reaction is called the free energy of activation, or **activation energy ($E_A$)**
- Activation energy is often supplied in the form of thermal energy that the reactant molecules absorb from their surroundings

# Activation Energy



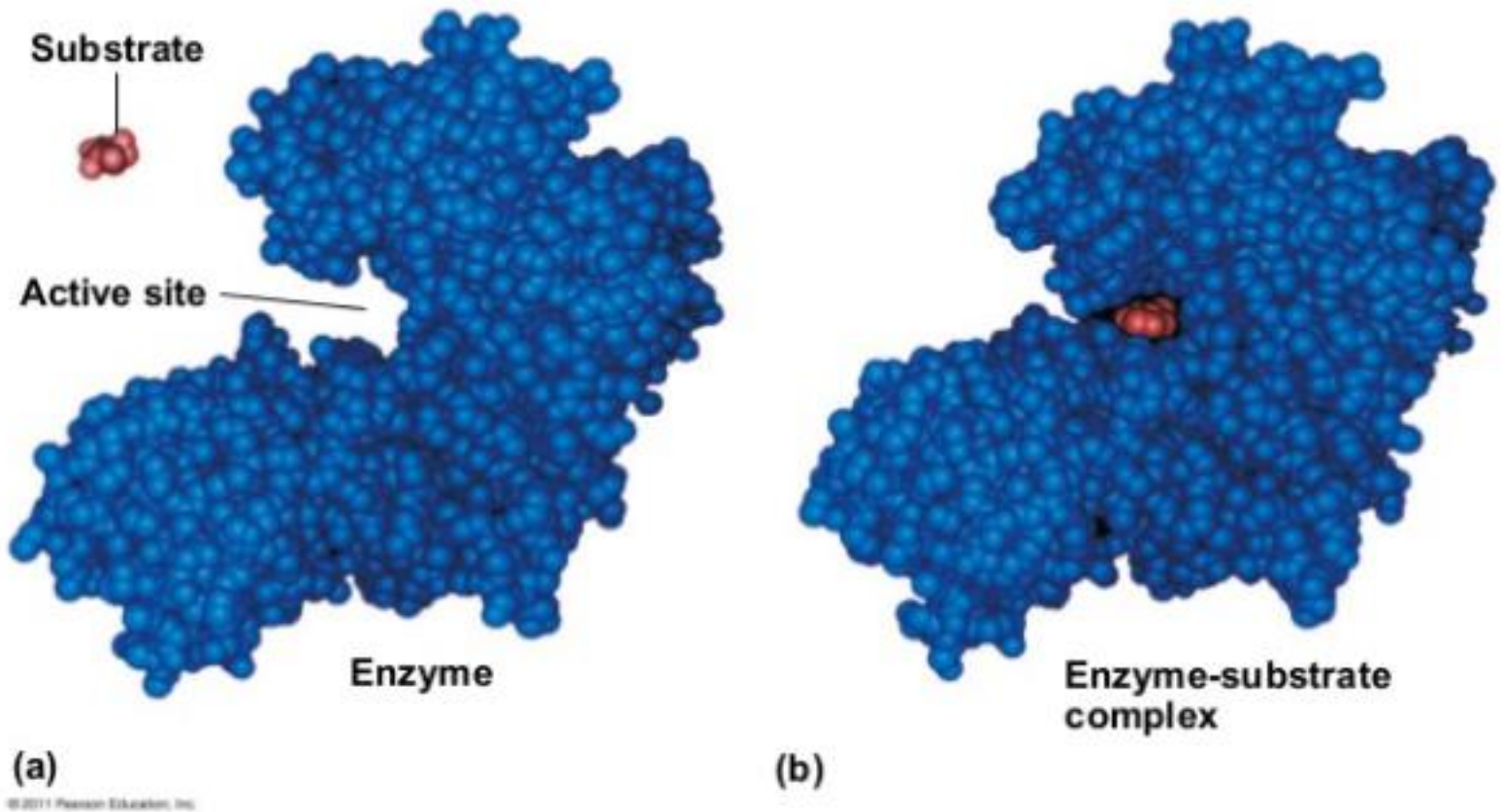
# How Enzymes Lower the $E_A$ Barrier

- Enzymes catalyze reactions by lowering the $E_A$ barrier
- Enzymes do not affect the change in free energy ($\Delta G$); instead, they hasten reactions that would occur eventually


Course of reaction without enzyme
$E_A$ without enzyme
$E_A$ with enzyme is lower
Reactants
Course of reaction with enzyme
$\Delta G$ is unaffected by enzyme
Products
Free energy
Progress of the reaction

# Substrate Specificity of Enzymes

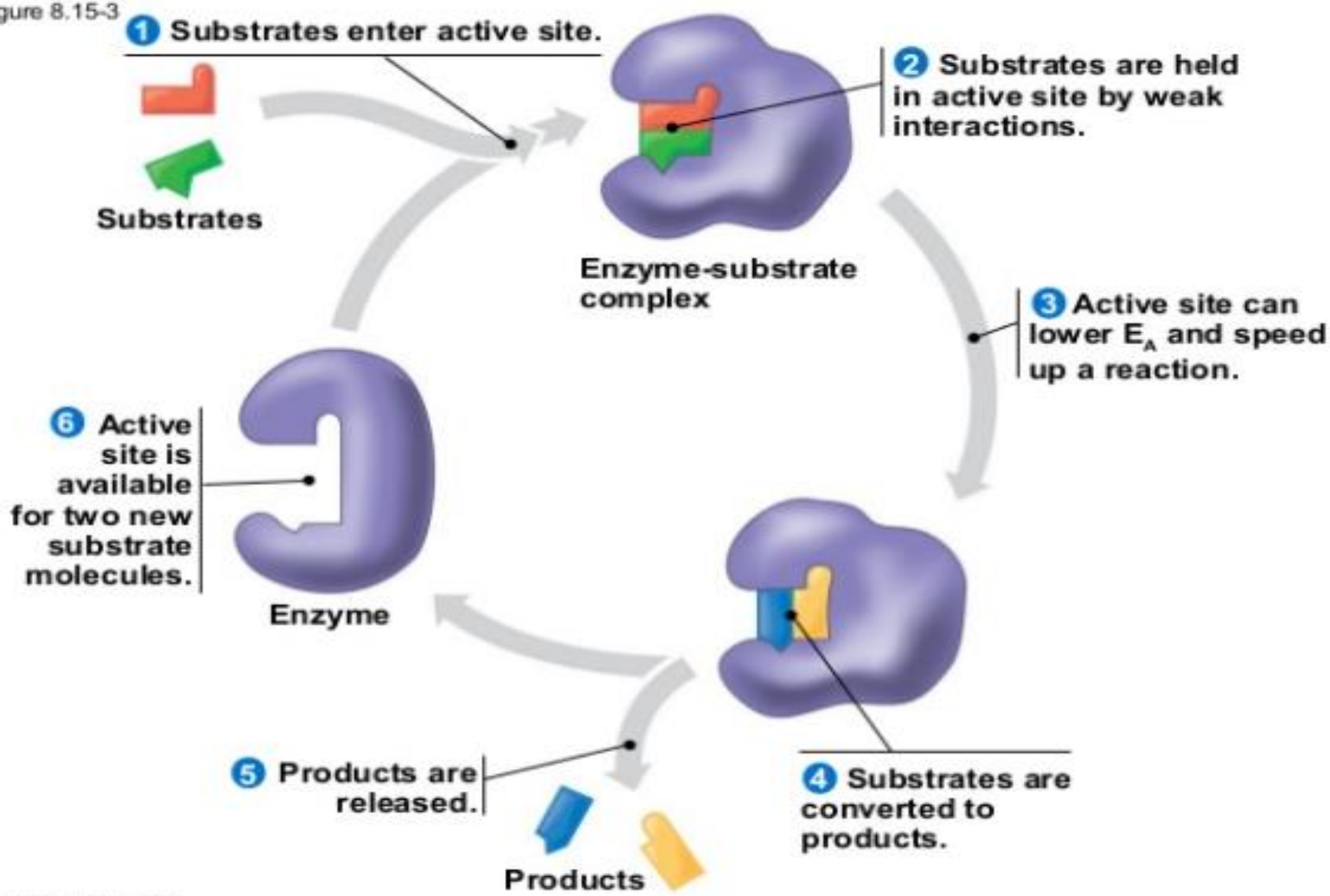
- The reactant that an enzyme acts on is called the enzyme's **substrate**
- The enzyme binds to its substrate, forming an **enzyme-substrate complex**
- The **active site** is the region on the enzyme where the substrate binds
- **Induced fit** of a substrate brings chemical groups of the active site into positions that enhance their ability to catalyze the reaction



# Catalysis in the Enzyme's Active Site

- In an enzymatic reaction, the substrate binds to the active site of the enzyme
- The active site can lower an $E_A$ barrier by
  - Orienting substrates correctly
  - Straining substrate bonds
  - Providing a favorable microenvironment
  - Covalently bonding to the substrate

Figure 8.15-3

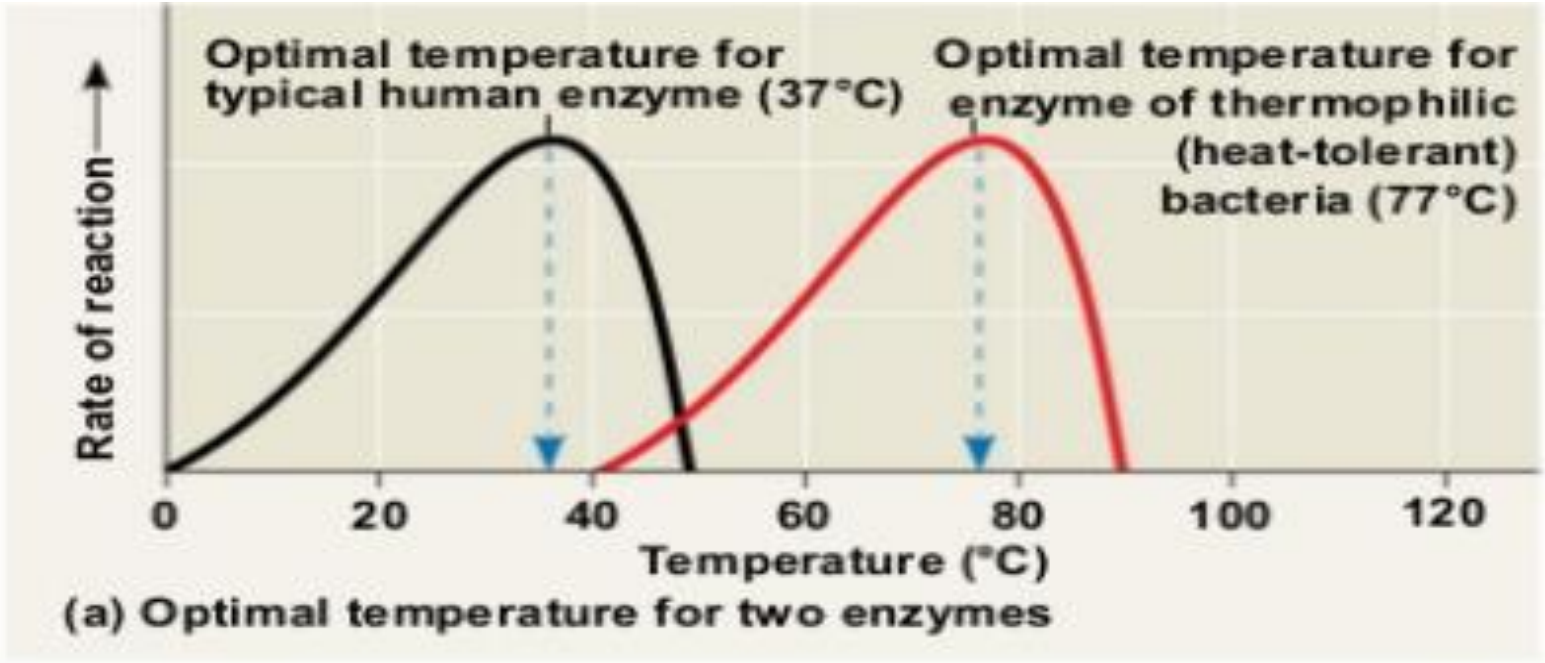

1 Substrates enter active site.
Substrates
2 Substrates are held in active site by weak interactions.
Enzyme-substrate complex
3 Active site can lower $E_A$ and speed up a reaction.
4 Substrates are converted to products.
5 Products are released.
Products
6 Active site is available for two new substrate molecules.
Enzyme

# Effects of Local Conditions on Enzyme Activity

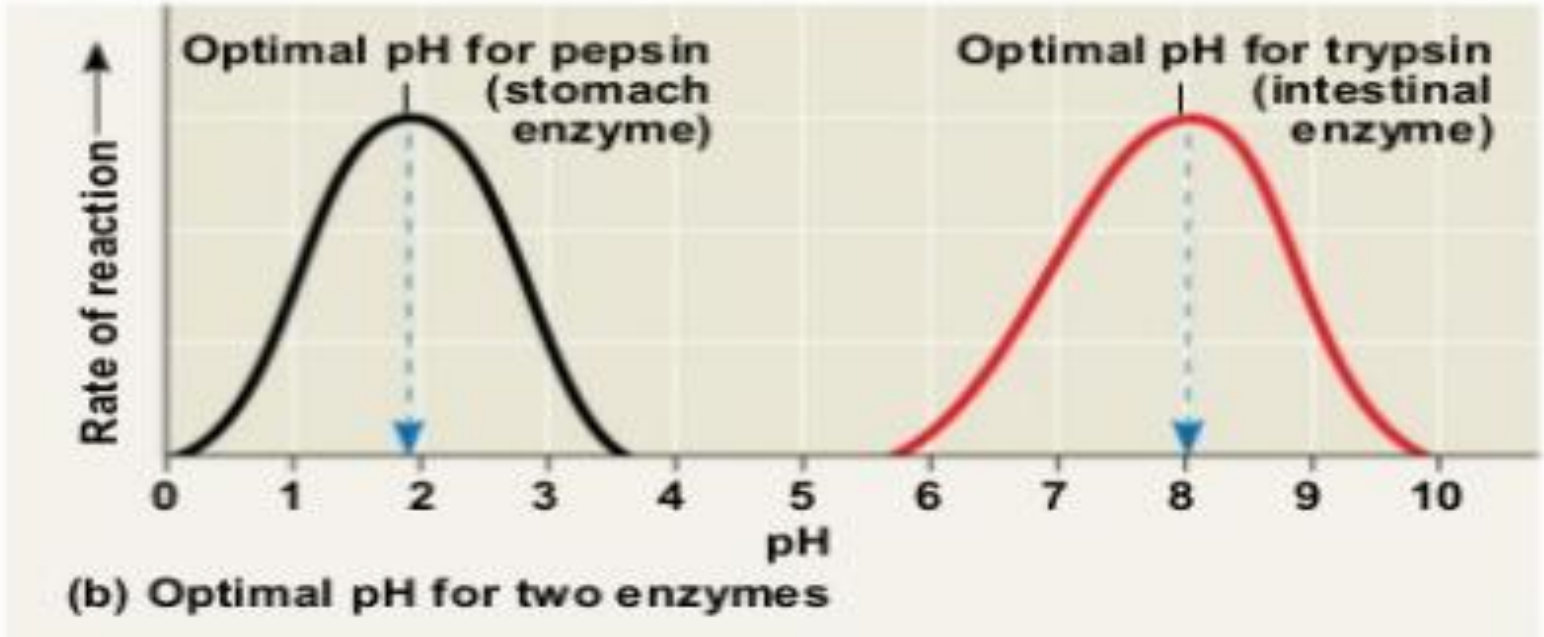
- An enzyme's activity can be affected by
  - General environmental factors, such as temperature and pH
  - Chemicals that specifically influence the enzyme

# *Effects of Temperature and pH*

- Each enzyme has an optimal temperature in which it can function
- Each enzyme has an optimal pH in which it can function
- Optimal conditions favor the most active shape for the enzyme molecule




(a) Optimal temperature for two enzymes



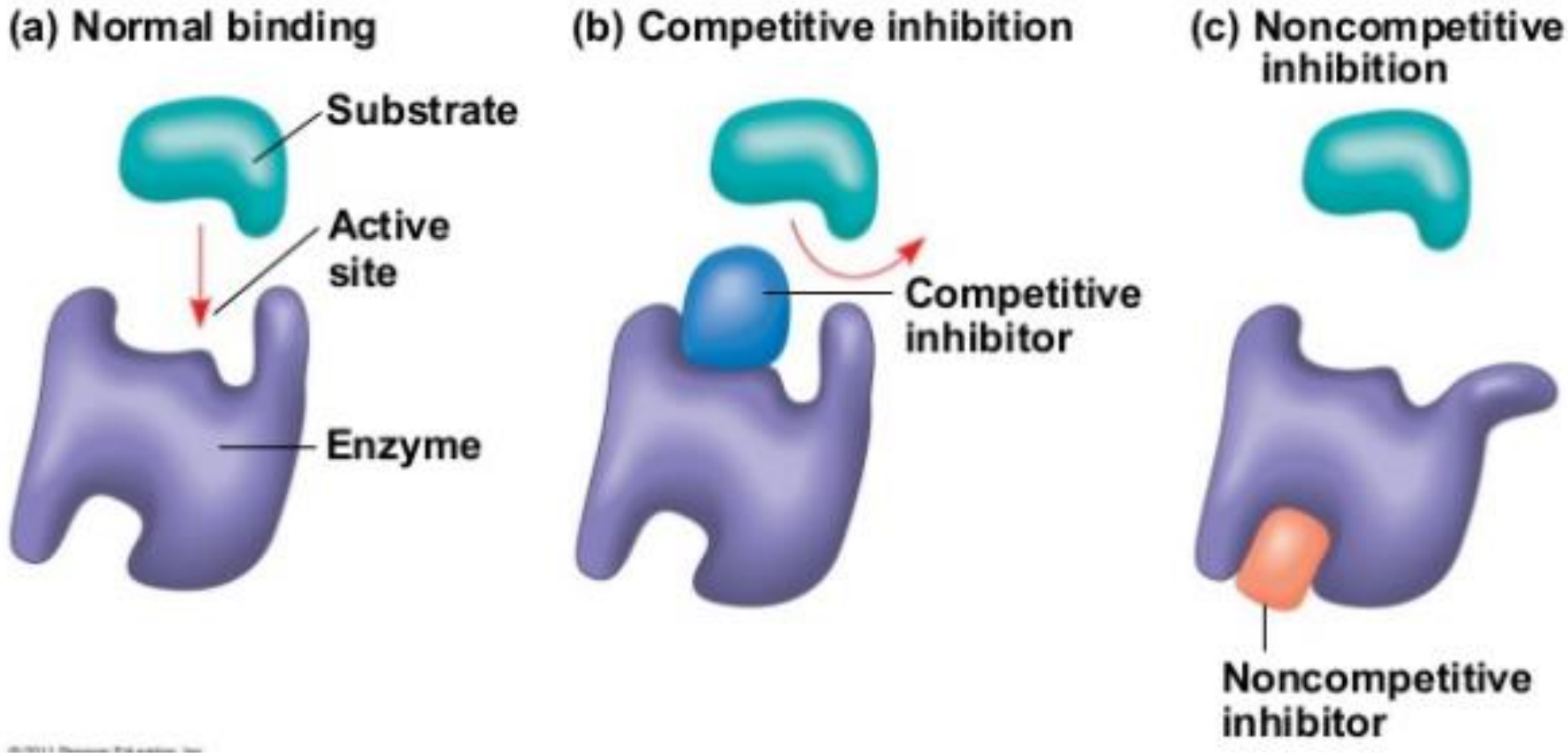

(b) Optimal pH for two enzymes

# *Cofactors*

- **Cofactors** are nonprotein enzyme helpers
- Cofactors may be inorganic (such as a metal in ionic form) or organic
- An organic cofactor is called a **coenzyme**
- Coenzymes include vitamins

# *Enzyme Inhibitors*

- **Competitive inhibitors** bind to the active site of an enzyme, competing with the substrate
- **Noncompetitive inhibitors** bind to another part of an enzyme, causing the enzyme to change shape and making the active site less effective
- Examples of inhibitors include toxins, poisons, pesticides, and antibiotics


(a) Normal binding
Substrate
Active site
Enzyme
(b) Competitive inhibition
Competitive inhibitor
(c) Noncompetitive inhibition
Noncompetitive inhibitor

# Regulation of enzyme activity helps control metabolism

- Chemical chaos would result if a cell's metabolic pathways were not tightly regulated
- A cell does this by switching on or off the genes that encode specific enzymes or by regulating the activity of enzymes

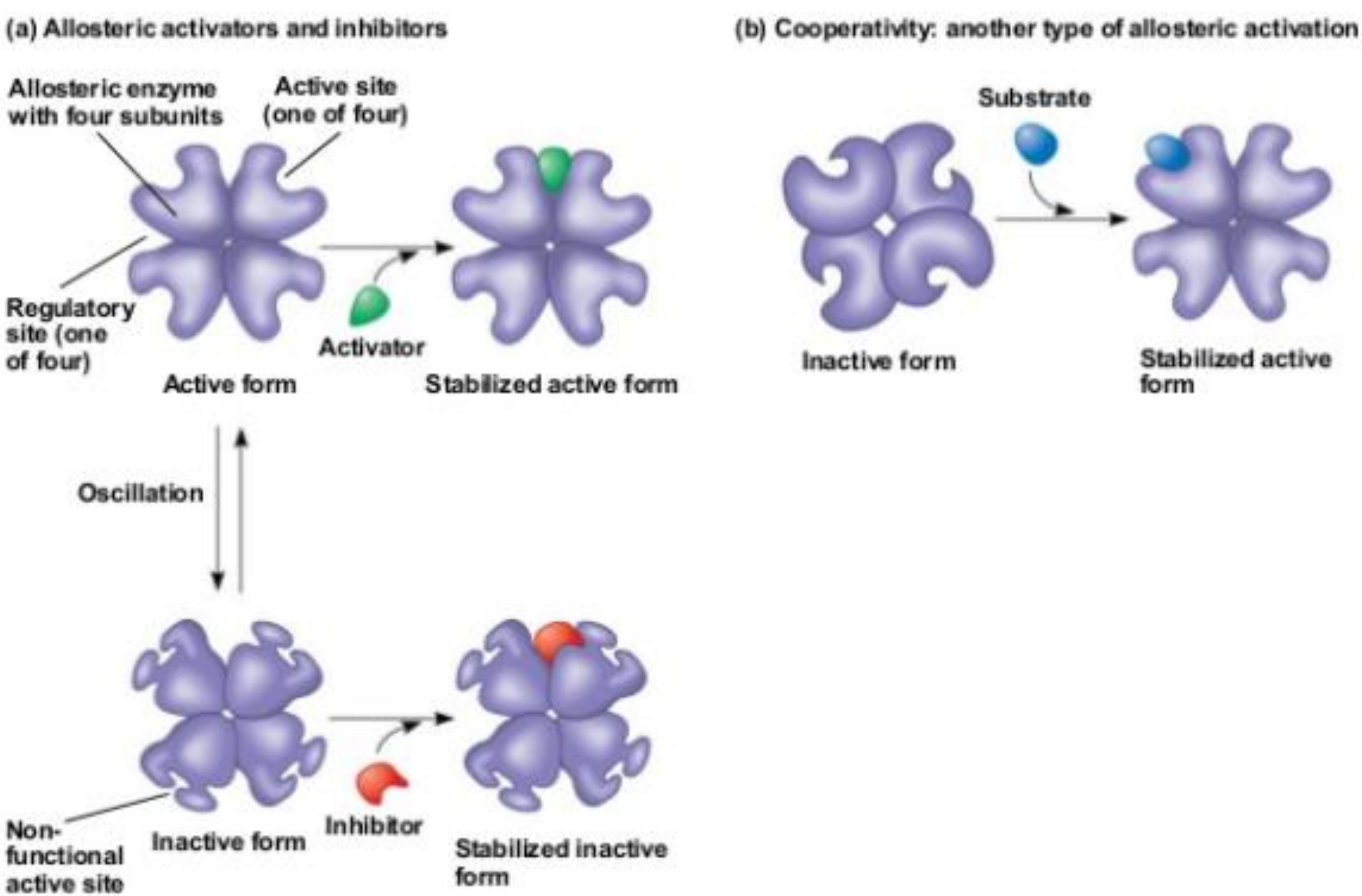
# Allosteric Regulation of Enzymes

- **Allosteric regulation** may either inhibit or stimulate an enzyme's activity
- Allosteric regulation occurs when a regulatory molecule binds to a protein at one site and affects the protein's function at another site

# *Allosteric Activation and Inhibition*

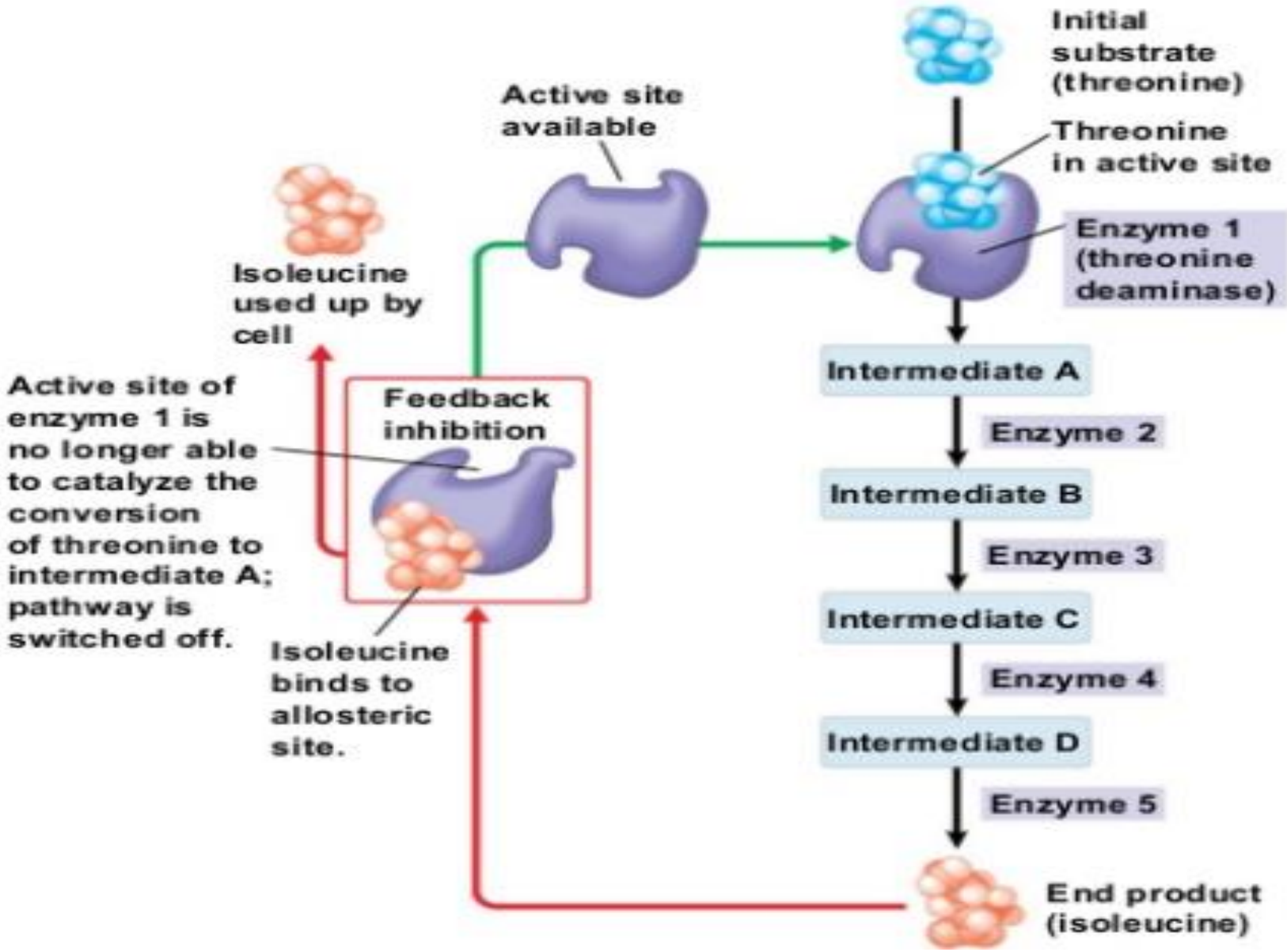
- Most allosterically regulated enzymes are made from polypeptide subunits
- Each enzyme has active and inactive forms
- The binding of an activator stabilizes the active form of the enzyme
- The binding of an inhibitor stabilizes the inactive form of the enzyme

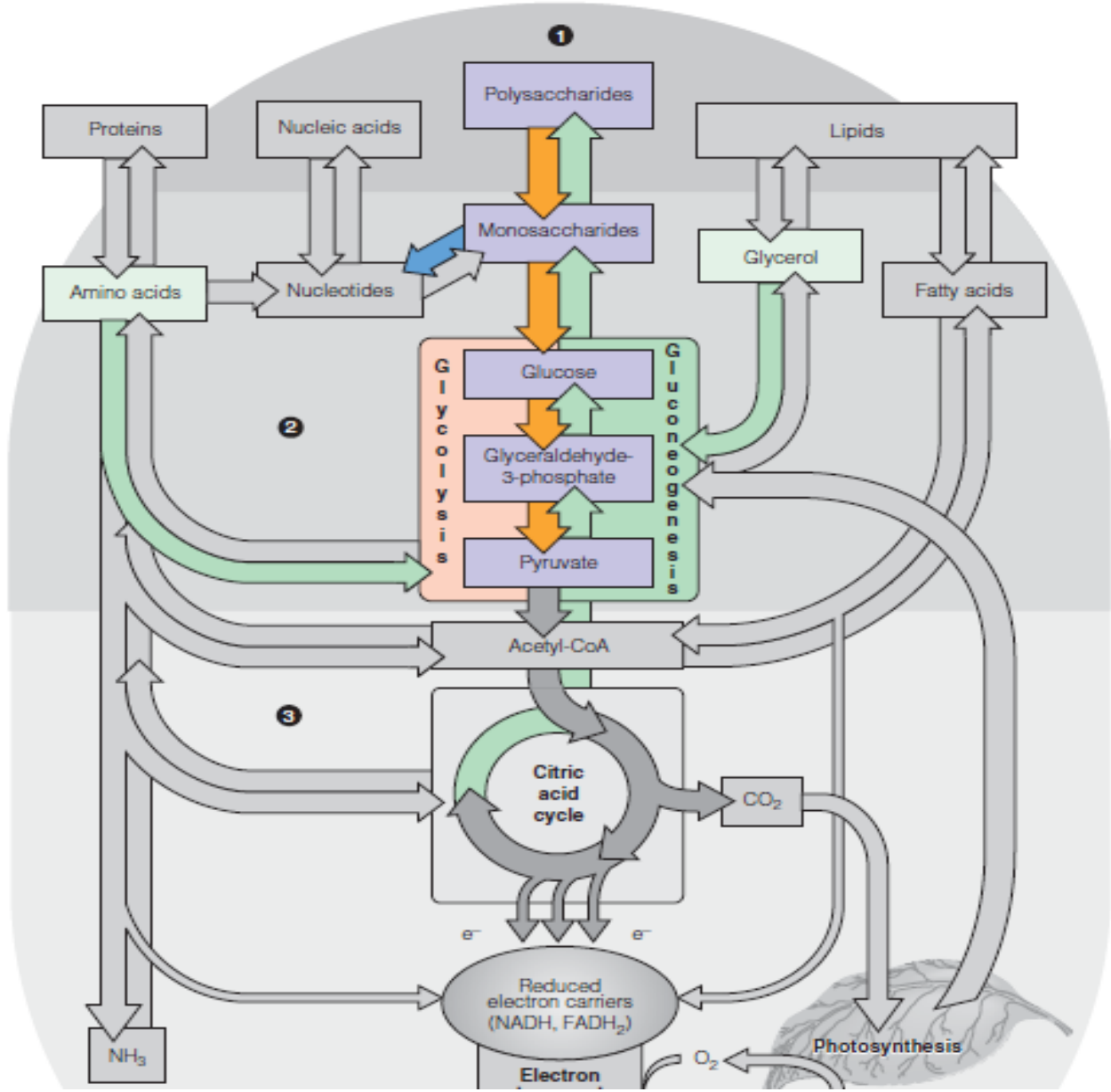
- **Cooperativity** is a form of allosteric regulation that can amplify enzyme activity
- One substrate molecule primes an enzyme to act on additional substrate molecules more readily
- Cooperativity is allosteric because binding by a substrate to one active site affects catalysis in a different active site

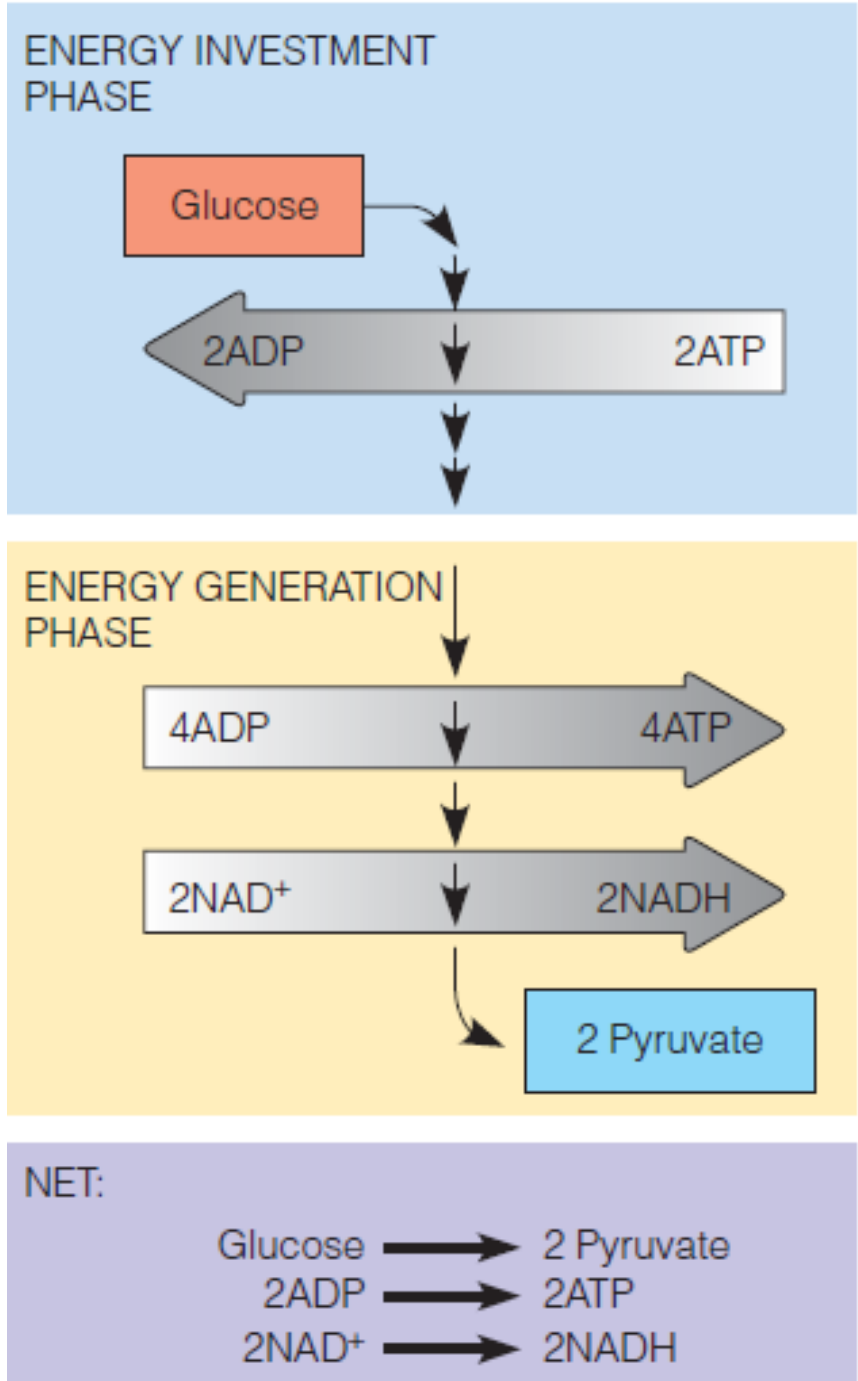

(a) Allosteric activators and inhibitors
Allosteric enzyme with four subunits
Active site (one of four)
Regulatory site (one of four)
Activator
Active form
Stabilized active form
Oscillation
Non-functional active site
Inactive form
Inhibitor
Stabilized inactive form
(b) Cooperativity: another type of allosteric activation
Substrate
Inactive form
Stabilized active form

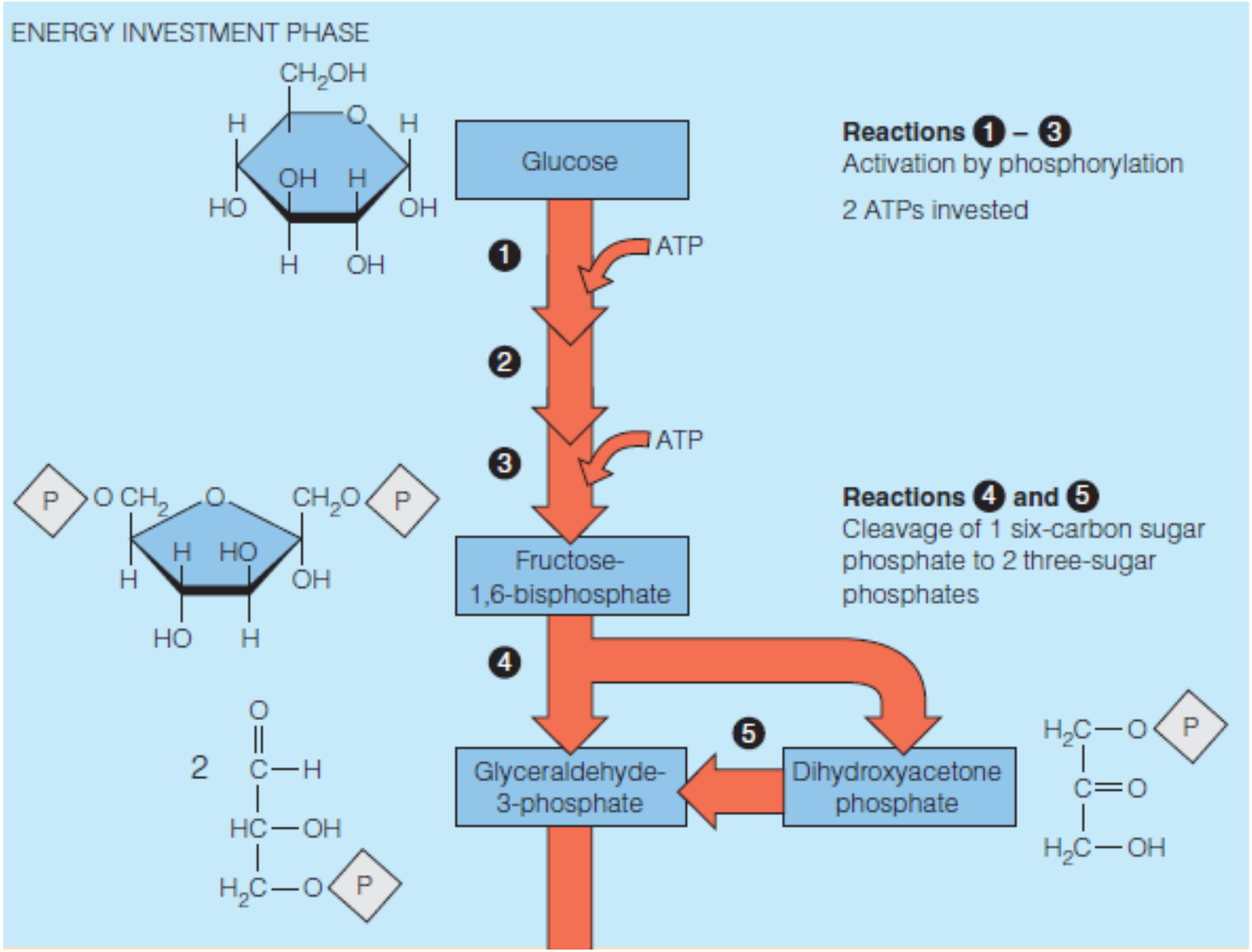
# *Feedback Inhibition*

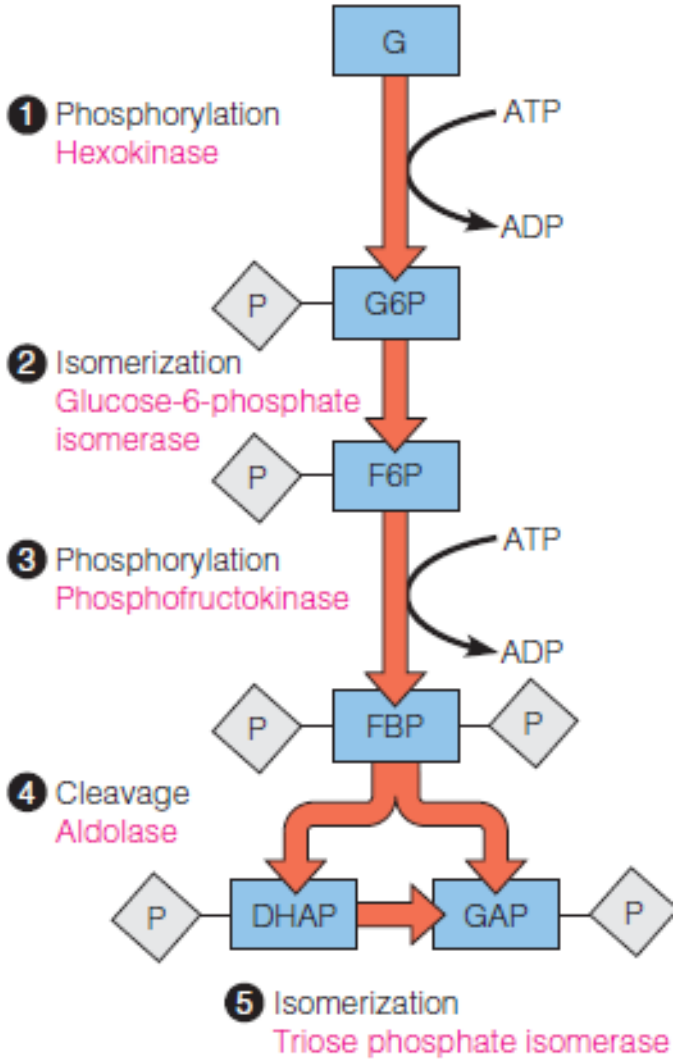
- In **feedback inhibition**, the end product of a metabolic pathway shuts down the pathway
- Feedback inhibition prevents a cell from wasting chemical resources by synthesizing more product than is needed

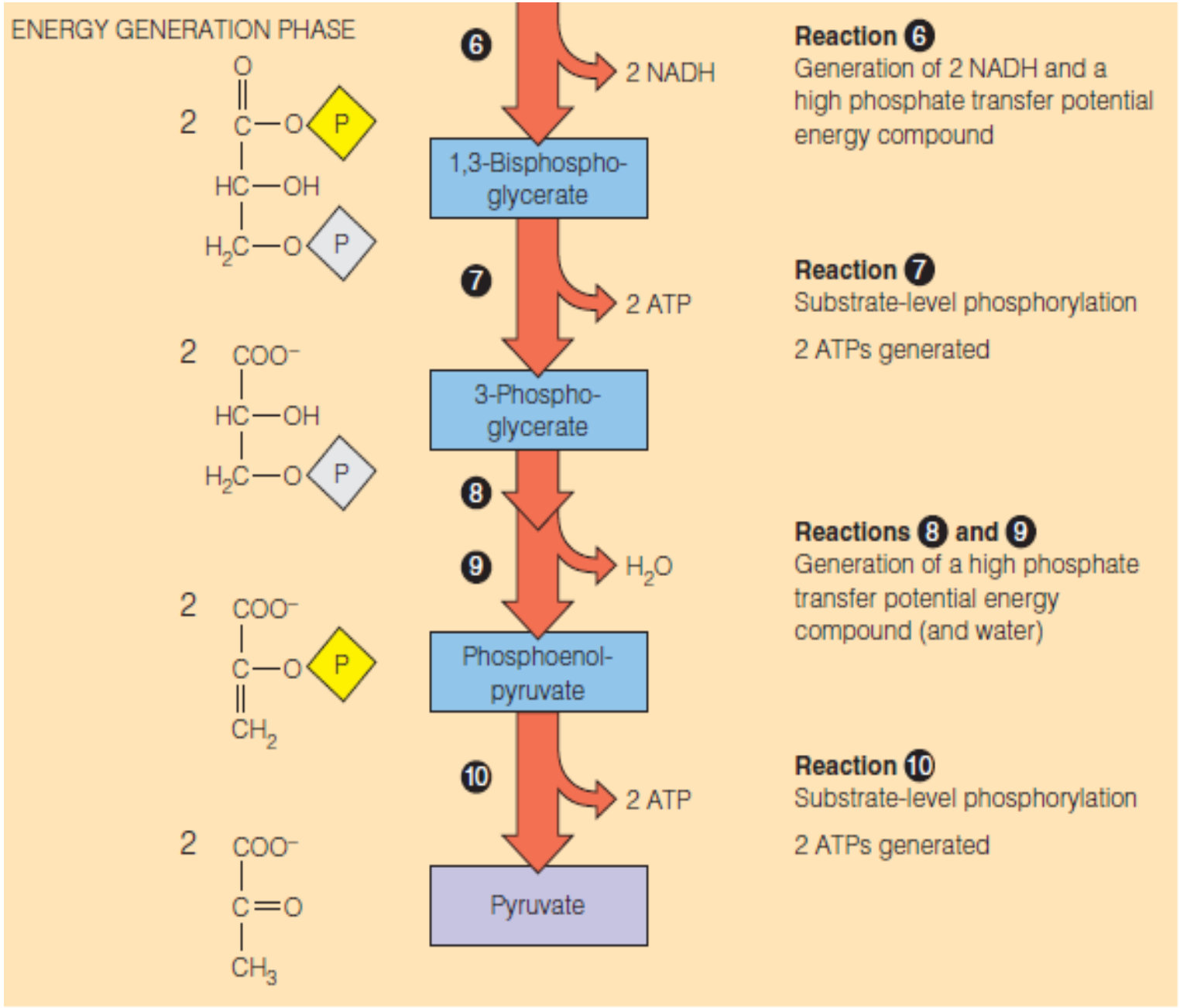

Initial substrate (threonine)
Active site available
Threonine in active site
Isoleucine used up by cell
Enzyme 1 (threonine deaminase)
Intermediate A
Active site of enzyme 1 is no longer able to catalyze the conversion of threonine to intermediate A; pathway is switched off.
Feedback inhibition
Enzyme 2
Intermediate B
Enzyme 3
Intermediate C
Isoleucine binds to allosteric site.
Enzyme 4
Intermediate D
Enzyme 5
End product (isoleucine)

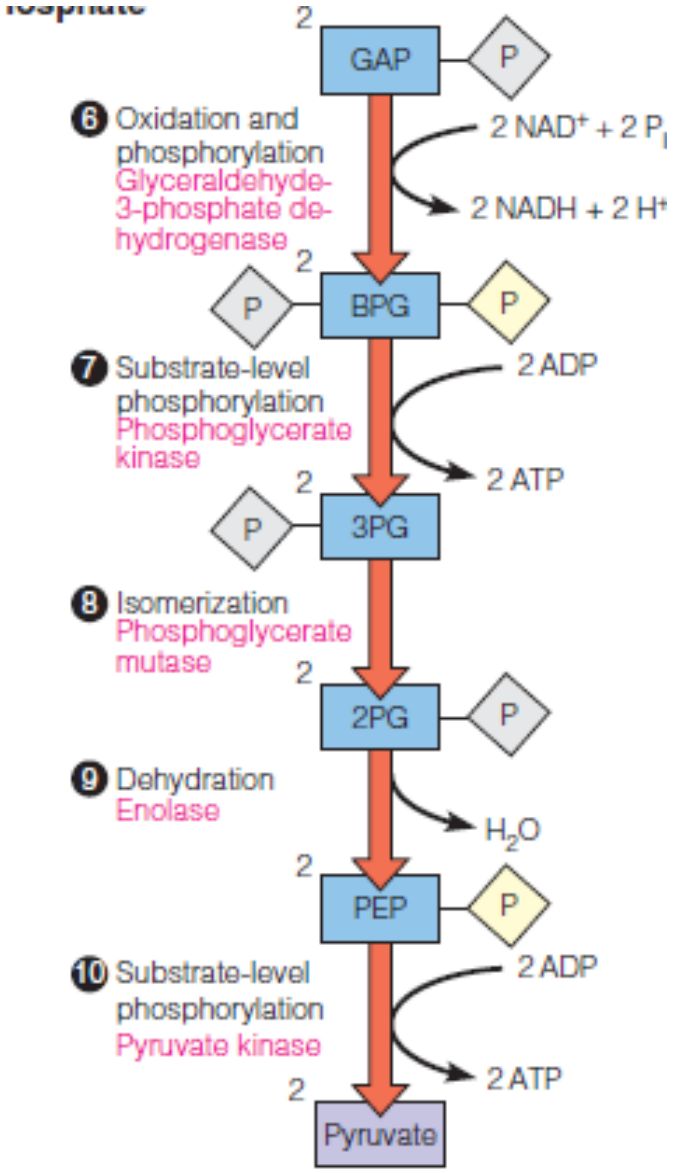

1
Polysaccharides
Proteins
Nucleic acids
Lipids
Monosaccharides
Glycerol
Amino acids
Nucleotides
Fatty acids
Glycolysis
Gluconeogenesis
Glucose
2
Glyceraldehyde-3-phosphate
Pyruvate
Acetyl-CoA
3
Citric acid cycle
$CO_2$
$e^-$
$e^-$
Reduced electron carriers ($NADH$, $FADH_2$)
$NH_3$
Electron
$O_2$
Photosynthesis

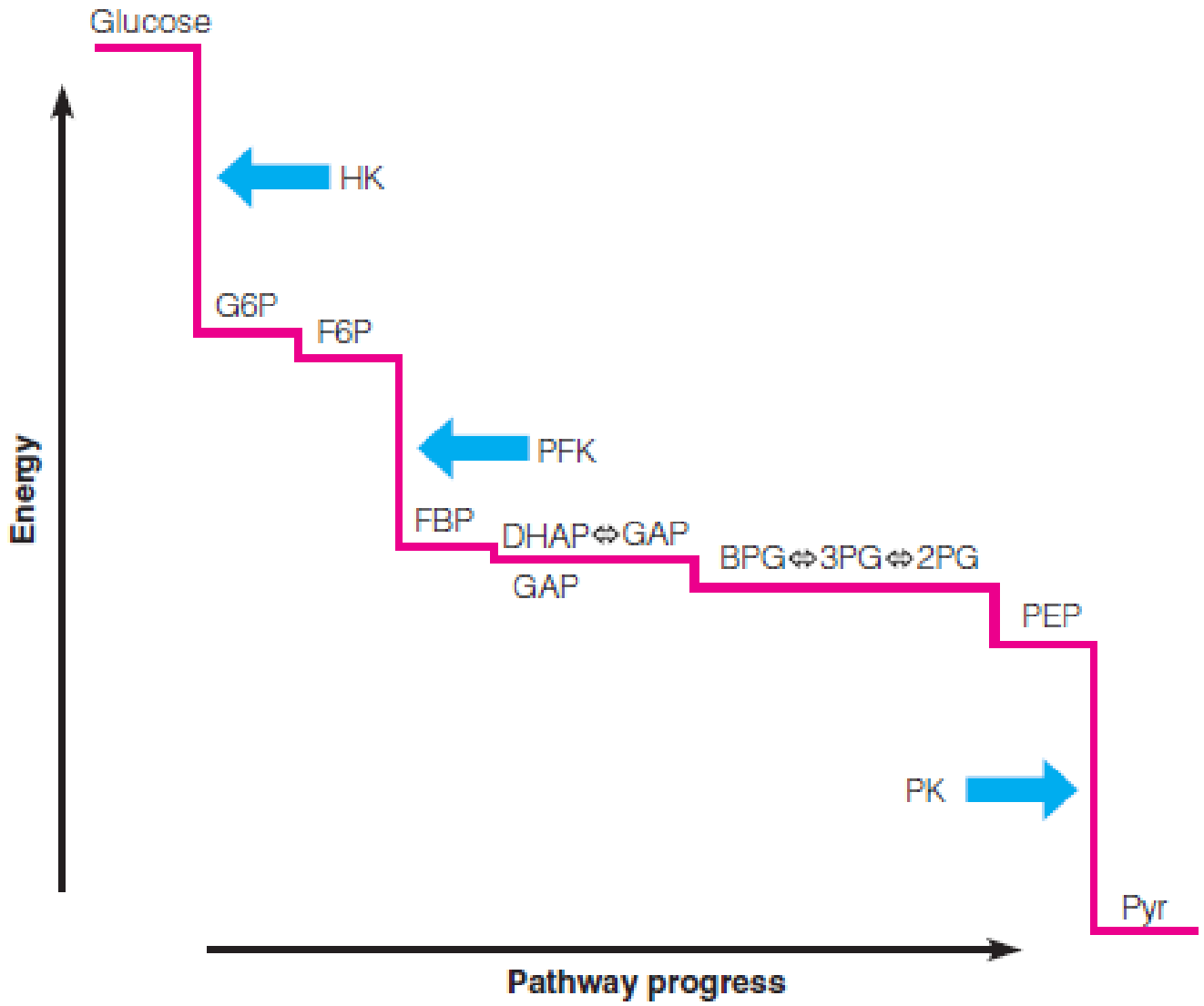

ENERGY INVESTMENT PHASE
Glucose
2ADP
2ATP
ENERGY GENERATION PHASE
4ADP
4ATP
2NAD+
2NADH
2 Pyruvate
NET:
Glucose → 2 Pyruvate
2ADP → 2ATP
2NAD+ → 2NADH


ENERGY INVESTMENT PHASE
Glucose
ATP
ATP
Fructose-1,6-bisphosphate
Glyceraldehyde-3-phosphate
Dihydroxyacetone phosphate
Reactions 1 – 3
Activation by phosphorylation
2 ATPs invested
Reactions 4 and 5
Cleavage of 1 six-carbon sugar phosphate to 2 three-sugar phosphates

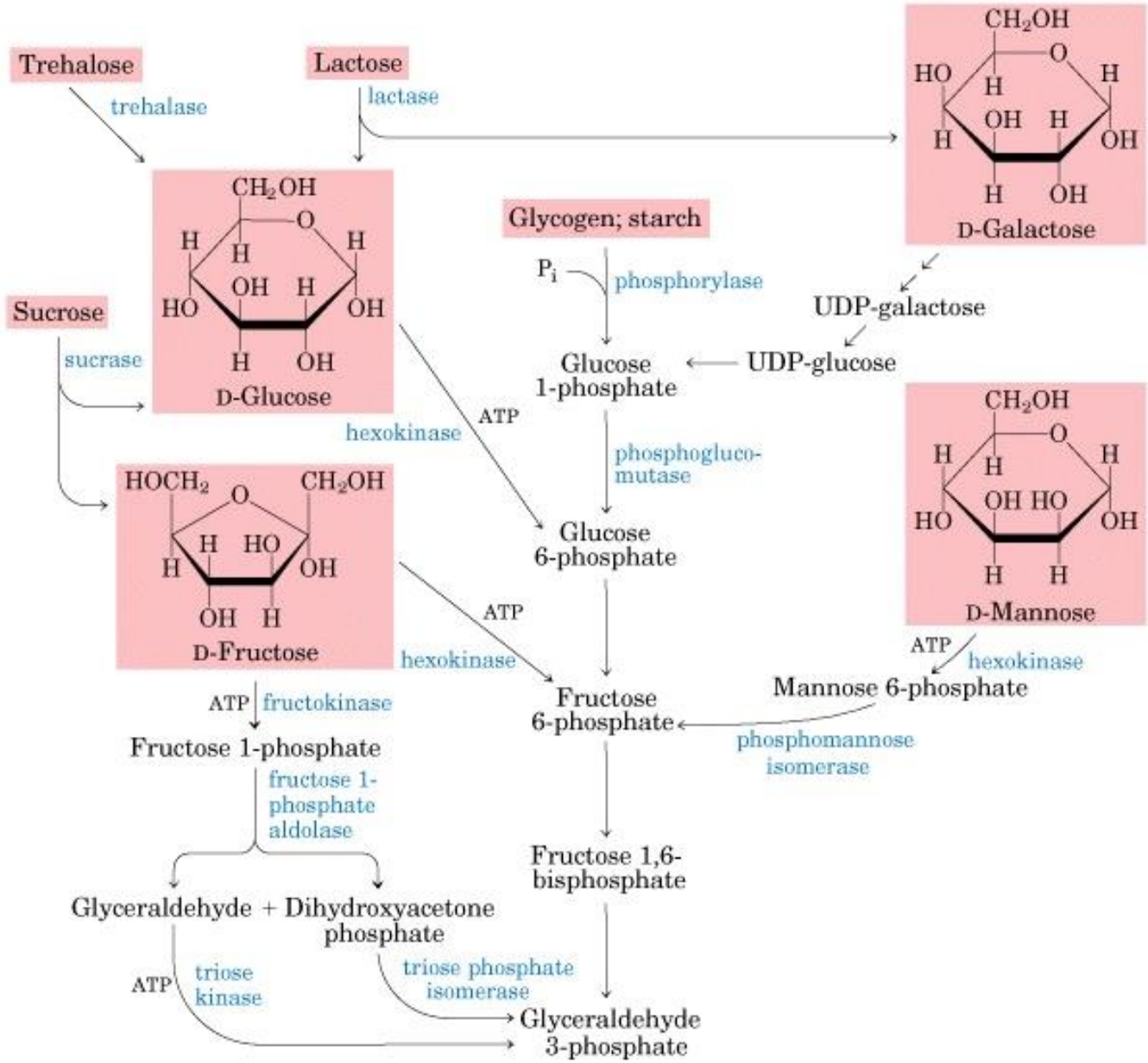

G
1 Phosphorylation
Hexokinase
ATP
ADP
G6P
2 Isomerization
Glucose-6-phosphate isomerase
F6P
3 Phosphorylation
Phosphofructokinase
ATP
ADP
FBP
4 Cleavage
Aldolase
DHAP
GAP
5 Isomerization
Triose phosphate isomerase


ENERGY GENERATION PHASE
2
O
C—O
P
HC—OH
H2C—O
P
2 NADH
1,3-Bisphospho-glycerate
2 ATP
3-Phospho-glycerate
H2O
Phosphoenol-pyruvate
2 ATP
Pyruvate
COO⁻
CH2
CH3
Reaction 6
Generation of 2 NADH and a high phosphate transfer potential energy compound
Reaction 7
Substrate-level phosphorylation
2 ATPs generated
Reactions 8 and 9
Generation of a high phosphate transfer potential energy compound (and water)
Reaction 10
Substrate-level phosphorylation
2 ATPs generated


2
GAP
P
6 Oxidation and phosphorylation
Glyceraldehyde-3-phosphate de-hydrogenase
2 NAD+ + 2 Pi
2 NADH + 2 H+
BPG
7 Substrate-level phosphorylation
Phosphoglycerate kinase
2 ADP
2 ATP
3PG
8 Isomerization
Phosphoglycerate mutase
2PG
9 Dehydration
Enolase
H2O
PEP
10 Substrate-level phosphorylation
Pyruvate kinase
2 ADP
2 ATP
Pyruvate


Glucose
HK
G6P
F6P
PFK
FBP
DHAP⇔GAP
GAP
BPG⇔3PG⇔2PG
PEP
PK
Pyr
Energy
Pathway progress

# In Summary


Trehalose
trehalase
Lactose
lactase
D-Galactose
Glycogen; starch
$P_i$
phosphorylase
UDP-galactose
UDP-glucose
Glucose 1-phosphate
Sucrose
sucrase
D-Glucose
hexokinase
ATP
phosphogluco-mutase
Glucose 6-phosphate
D-Mannose
D-Fructose
ATP
hexokinase
ATP
hexokinase
Mannose 6-phosphate
ATP
fructokinase
Fructose 6-phosphate
phosphomannose isomerase
Fructose 1-phosphate
fructose 1-phosphate aldolase
Fructose 1,6-bisphosphate
Glyceraldehyde + Dihydroxyacetone phosphate
ATP
triose kinase
triose phosphate isomerase
Glyceraldehyde 3-phosphate

# Regulation of Glycolysis

| **Enzyme** | **Activator** |
| --- | --- |
| Hexokinase | AMP/ADP |
| Phosphofructokinase | AMP/ADP, Fructose-2,6-bisphosphate |
| Pyruvte kinase | AMP/ADP Fructose-1,6-bisphosphate |

| **Enzyme** | **Inhibitor** |
| --- | --- |
| Hexokinase | Glucose-6-phosphate |
| Phosphofructokinase | ATP, Citrate |
| Pyruvate kinase | ATP, Acetyl CoA, Alanine |

# Regulation of Hexokinase

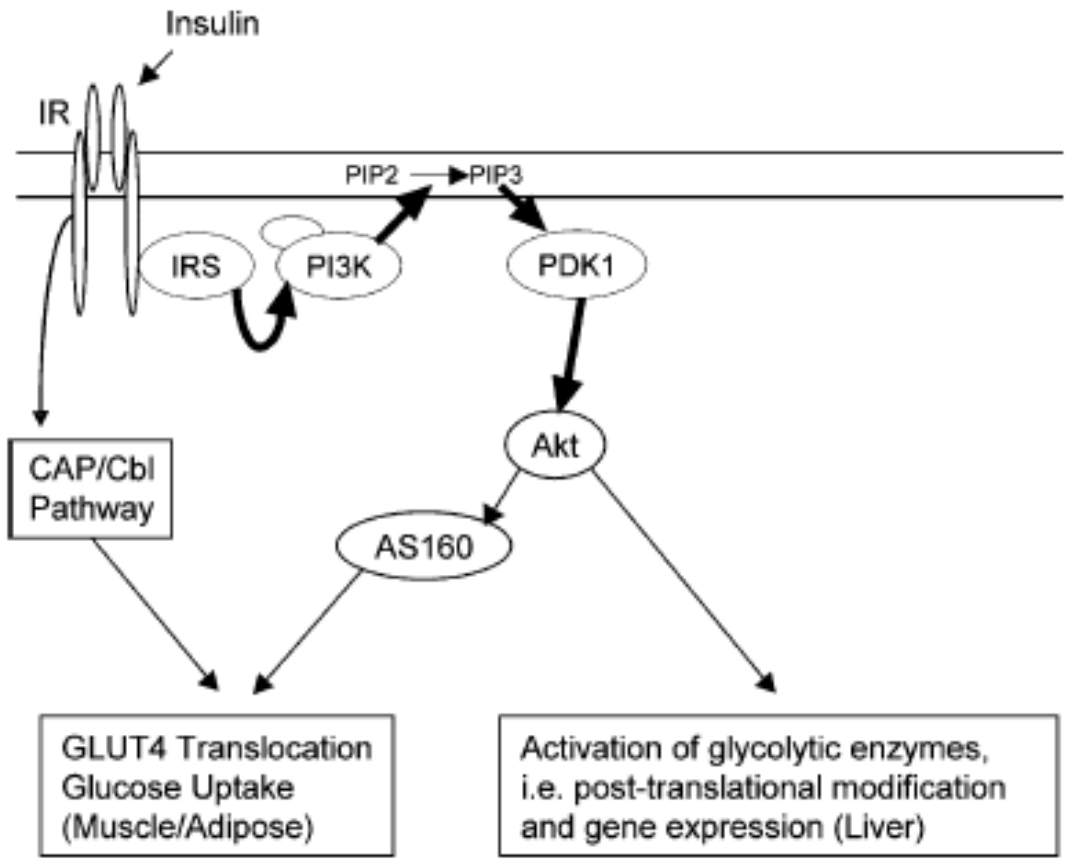
- Hexokinase catalyzed phosphorylation of glucose is the first irreversible step of glycolysis
- Regulated only by excess glucose-6-phosphate. If G6P accumulates in the cell, there is feedback inhibition of hexokinase till the G6P is consumed.
- Glucose-6-phosphate is required for other pathways including the pentose phosphate shunt and glycogen synthesis. So hexokinase step is not inhibited unless G-6-P accumulates. (no regulation by downstream intermediates / products of metabolism)
- Actually, liver, the site of glycogen synthesis, has a homologous enzyme called glucokinase. This has a high $K_M$ for glucose. This allows brain and muscle to utilize glucose prior to its storage as glycogen

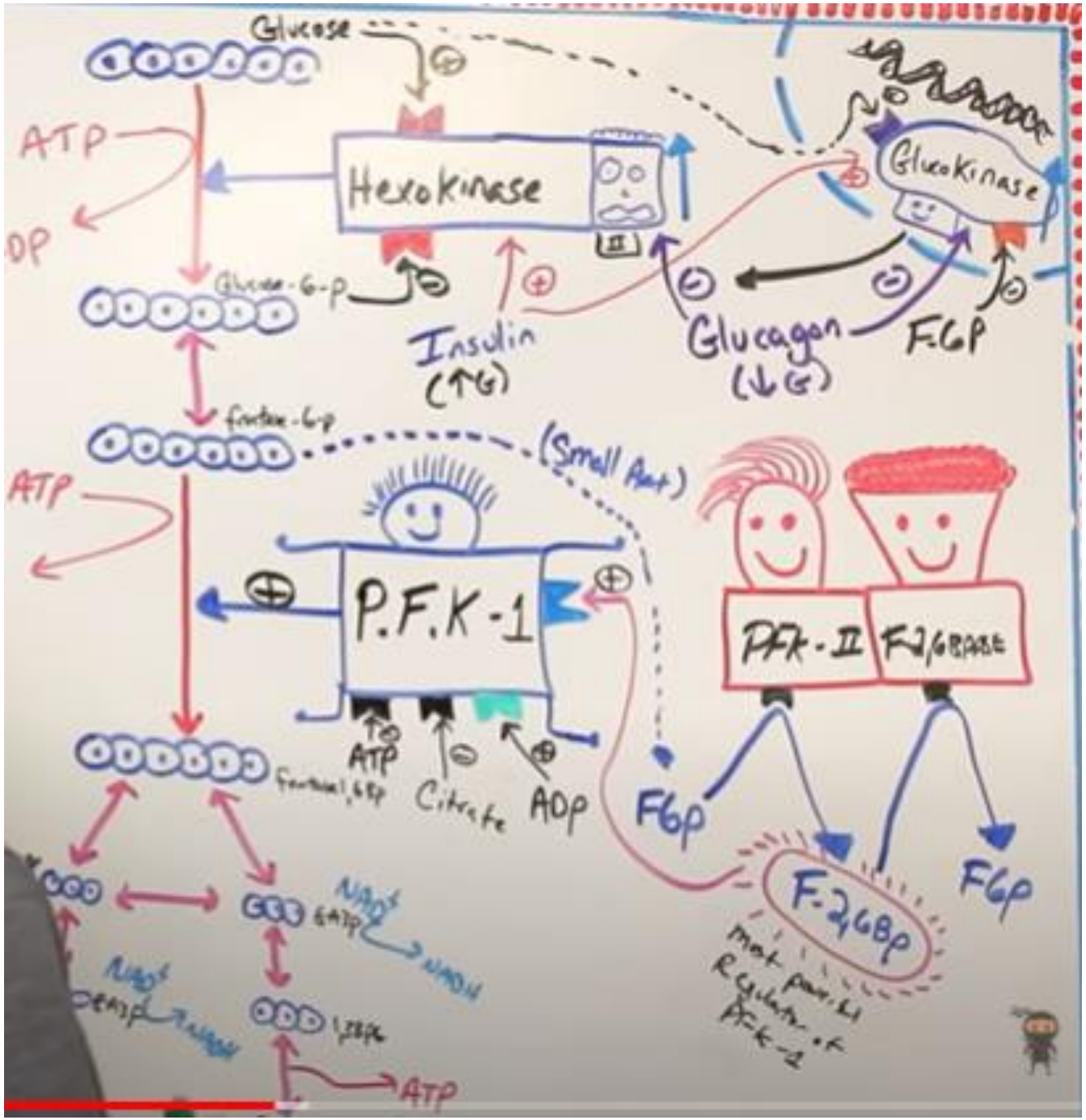
# Regulation of Phosphofructokinase

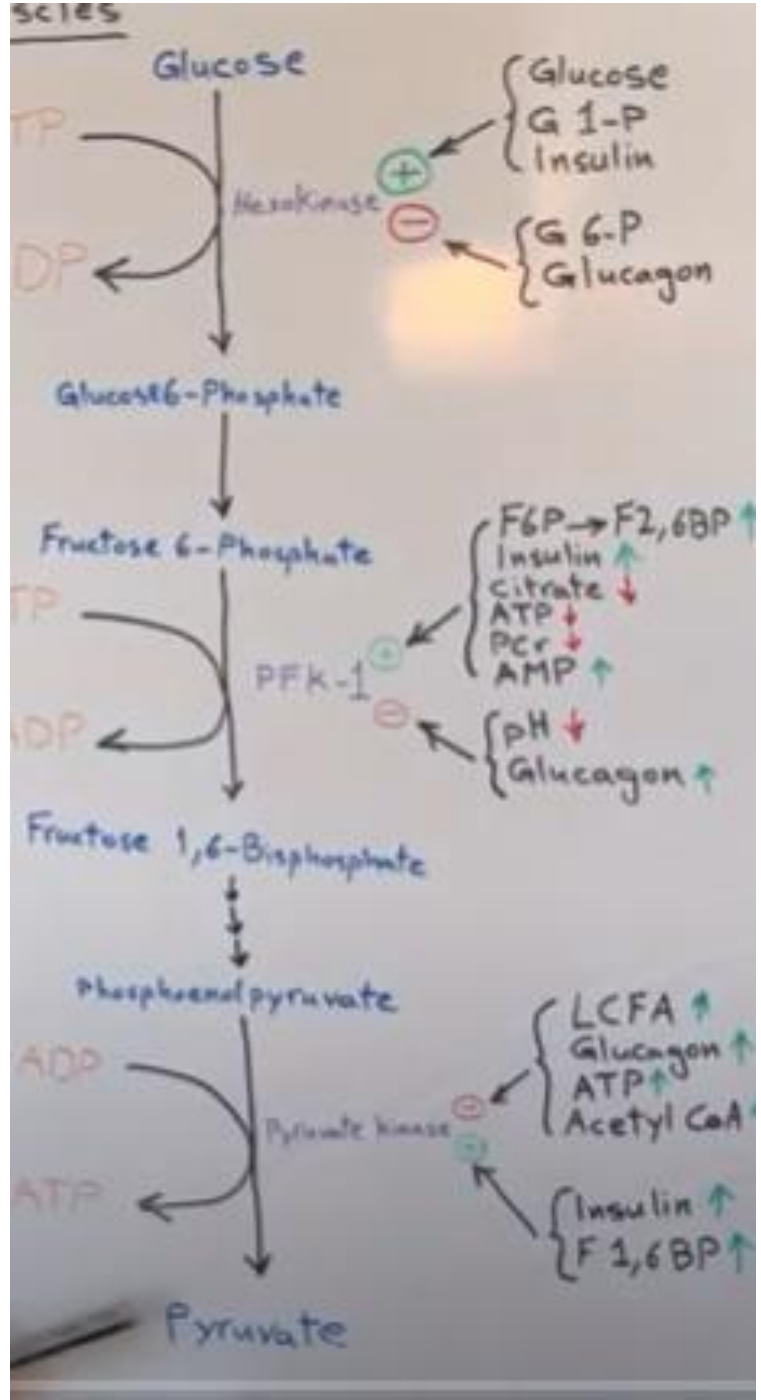
- The phosphofructokinase step is rate-limiting step of glycolysis.
- High AMP/ADP levels are activators of this enzyme, while high ATP levels are inhibitory (energy charge). In addition,
- Feed-back inhibition by Citrate, an intermediate of the TCA cycle.
- A major positive effector of phosphofructokinase is Fructose-2,6-bisphosphate. F-2,6-BP is formed by the hormone-stimulated phosphoylation of F-6-P. Thus, this is an example of allosteric feed-forward activation

# Regulation of pyruvate kinase

- If glycolysis gets past the phosphofructokinase step, then regulation is at the pyruvate kinase step.
- Pyruvate kinase activity is inhibited under low glucose conditions by covalent phosphorylation
- If fructose 1,6 bisphosphate is formed, it acts a allosteric feed-forward activator and drives the pyruvate kinase reaction forward.
- Other positive effectors are AMP and ADP while ATP is a negative effector.
- Alanine, an aminoacid derived from pyruvate, is a negative effector of catabolism. Alanine levels signal the anabolic state of a cell. High alanine levels indicate that the cell has enough starting material for anabolic reactions and so catabolism (which provides the ingredients for anabolism) can be paused.


Insulin
IR
PIP2
PIP3
IRS
PI3K
PDK1
Akt
CAP/Cbl
Pathway
AS160
GLUT4 Translocation
Glucose Uptake
(Muscle/Adipose)
Activation of glycolytic enzymes,
i.e. post-translational modification
and gene expression (Liver)


Glucose
ATP
Hexokinase
Glucokinase
Glucose-6-p
Insulin
(↑G)
Glucagon
(↓G)
F.6P
ATP
(Small Amt)
P.F.K-1
PFK-II
F2,6BPase
ATP
Citrate
ADP
F6P
F6P
F.2,6BP
ATP


Glucose
Glucose
G 1-P
Insulin
Hexokinase
G 6-P
Glucagon
Glucose 6-Phosphate
Fructose 6-Phosphate
F6P → F2,6BP
Insulin
citrate
ATP
Pcr
AMP
PFK-1
pH
Glucagon
Fructose 1,6-Bisphosphate
Phosphoenol pyruvate
LCFA
Glucagon
ATP
Acetyl CoA
Pyruvate kinase
Insulin
F 1,6 BP
Pyruvate

# Lecture 3 Metabolism Gluconeogenesis

Dr. Bilal J M Aldahham

# Introduction

- In mammals, some tissues depend almost completely on glucose for their metabolic energy. For the human brain and nervous system, as well as the erythrocytes, testes, renal medulla, and embryonic tissues, glucose from the blood is the sole or major fuel source.

- The brain alone requires about 120 g of glucose each day—more than half of all the glucose stored as glycogen in muscle and liver. However, the supply of glucose from these stores is not always sufficient; between meals and during longer fasts, or after vigorous exercise, glycogen is depleted

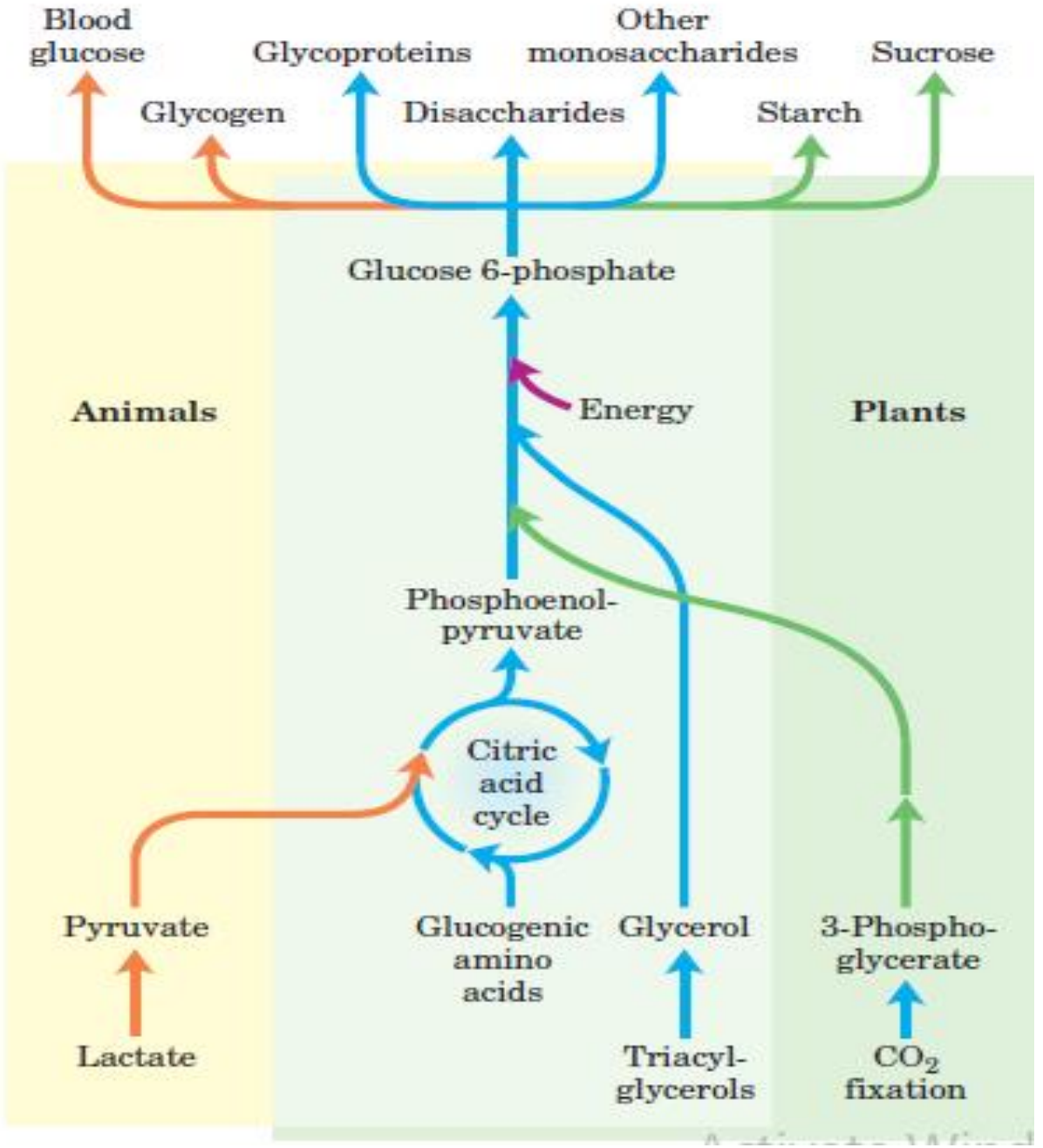
- For these times, organisms need a method for synthesizing glucose from noncarbohydrate precursors.

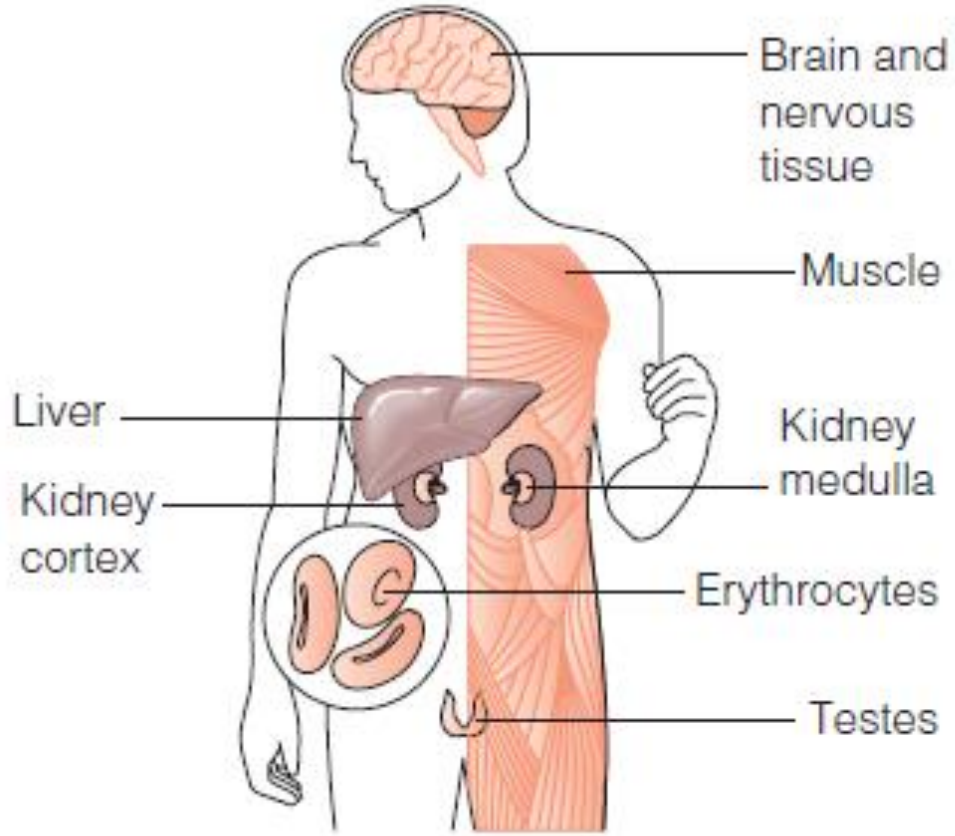
# Carbohydrate synthesis from simple precursors

Gluconeogenesis occurs in all animals, plants, fungi, and microorganisms. The reactions are essentially the same in all tissues and all species.

The important precursors of glucose in animals are three-carbon compounds such as lactate, pyruvate, and glycerol, as well as certain amino acids

In mammals, gluconeogenesis takes place mainly in the liver, and to a lesser extent in renal cortex.

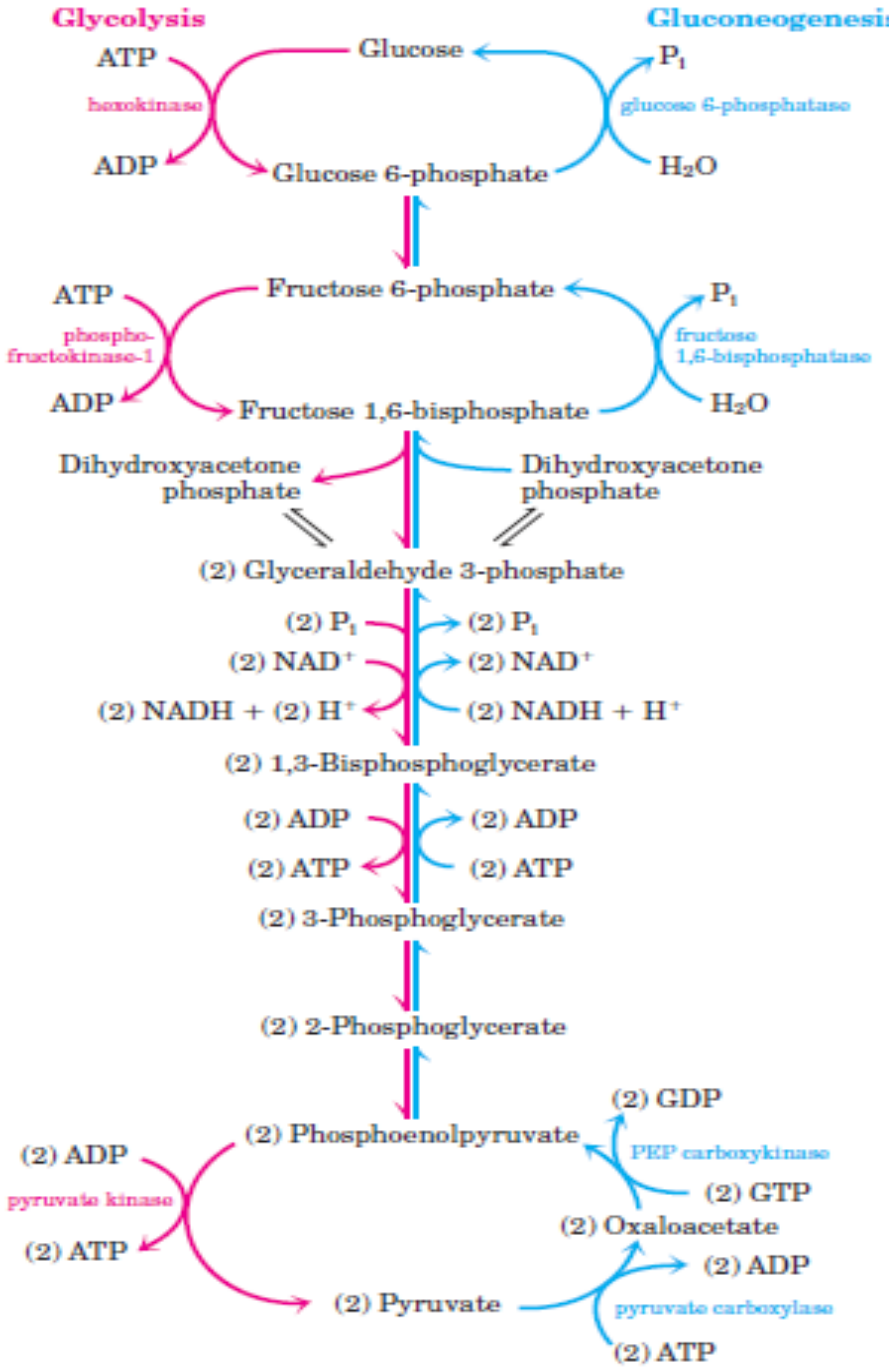





Tissues that synthesize glucose

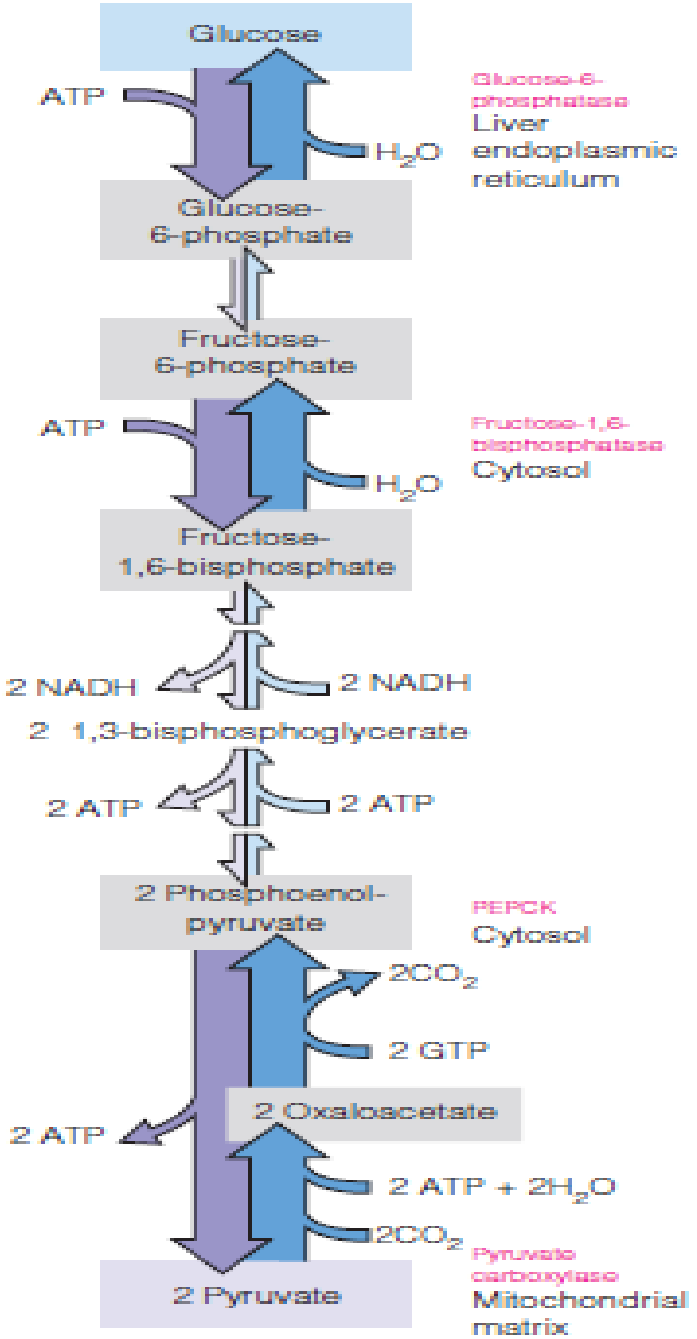
Tissues that use glucose as their primary energy source

# Opposing pathways of glycolysis and gluconeogenesis



# Reactions of glycolysis and gluconeogenesis

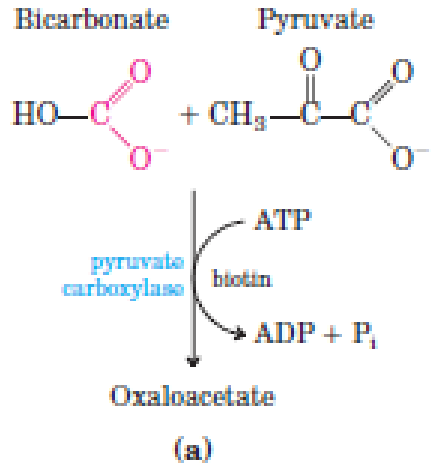
| Glycolysis Net: | Gluconeogenesis Net: |
| --- | --- |
| + 2ATP + 2NADH | – 4ATP – 2GTP – 2NADH |



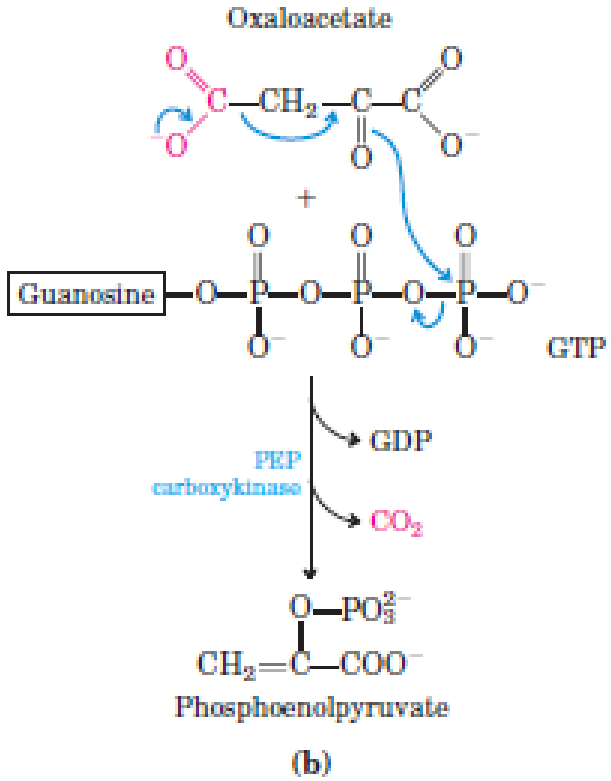
# Synthesis of phosphoenolpyruvate from pyruvate

**(a)** In mitochondria, pyruvate is converted to oxaloacetate in a biotinrequiring reaction catalyzed by pyruvate carboxylase

**(b)** In the cytosol, oxaloacetate is converted to phosphoenolpyruvate by PEP carboxykinase. The $CO_2$ incorporated in the pyruvate carboxylase reaction is lost here as $CO_2$. The decarboxylation leads to a rearrangement of electrons that facilitates attack of the carbonyl oxygen of the pyruvate moiety on the phosphate of GTP



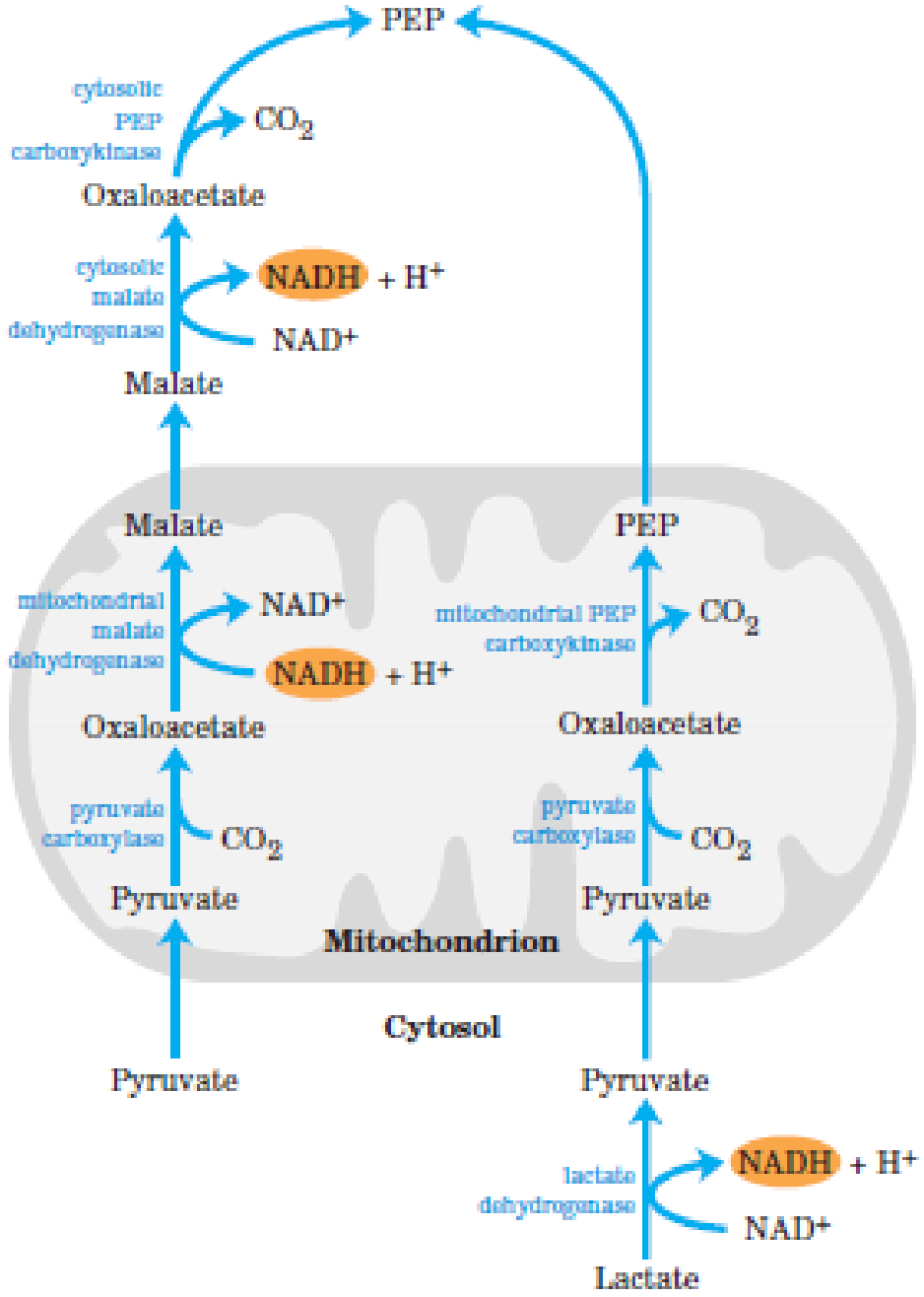

(a)




(b)

# Alternative paths from pyruvate to phosphoenolpyruvate

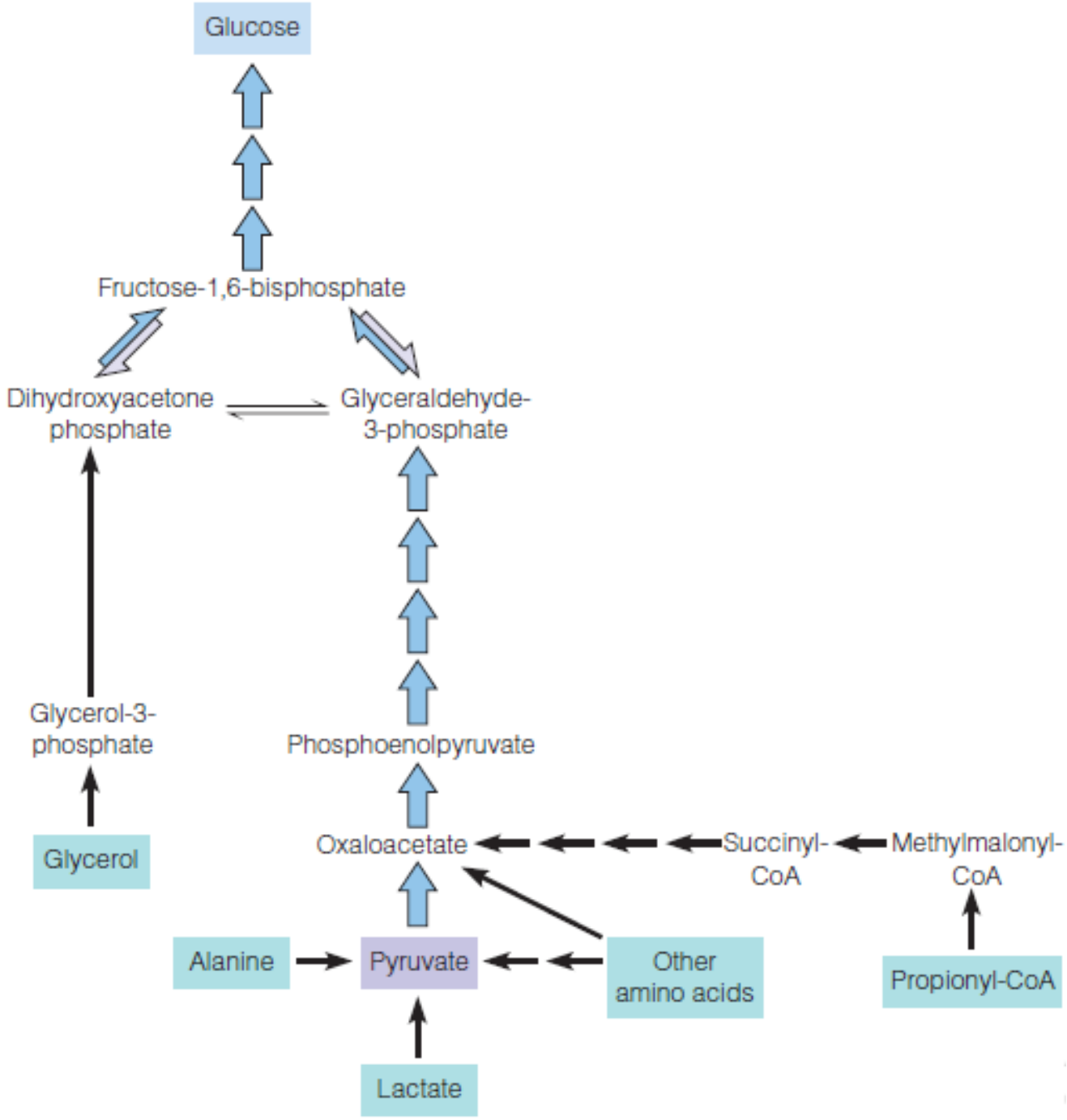
The path that predominates depends on the glucogenic precursor (lactate or pyruvate). The path on the right predominates when lactate is the precursor, because cytosolic NADH is generated in the lactate dehydrogenase reaction and does not have to be shuttled out of the mitochondrion (see text). The relative importance of the two pathways depends on the availability of lactate and the cytosolic requirements for NADH by gluconeogenesis.



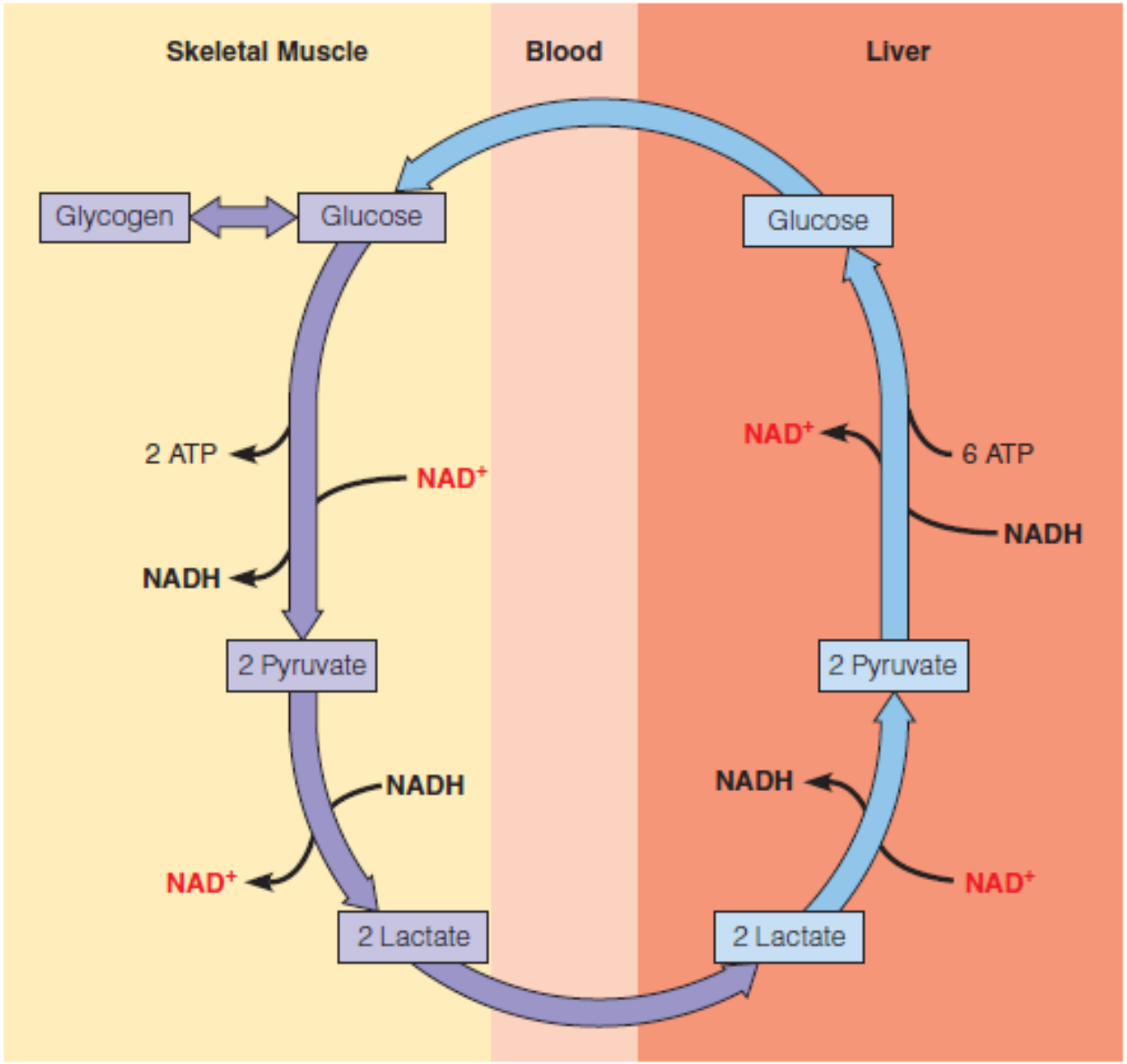
# Gluconeogenesis Is Energetically Expensive, but Essential

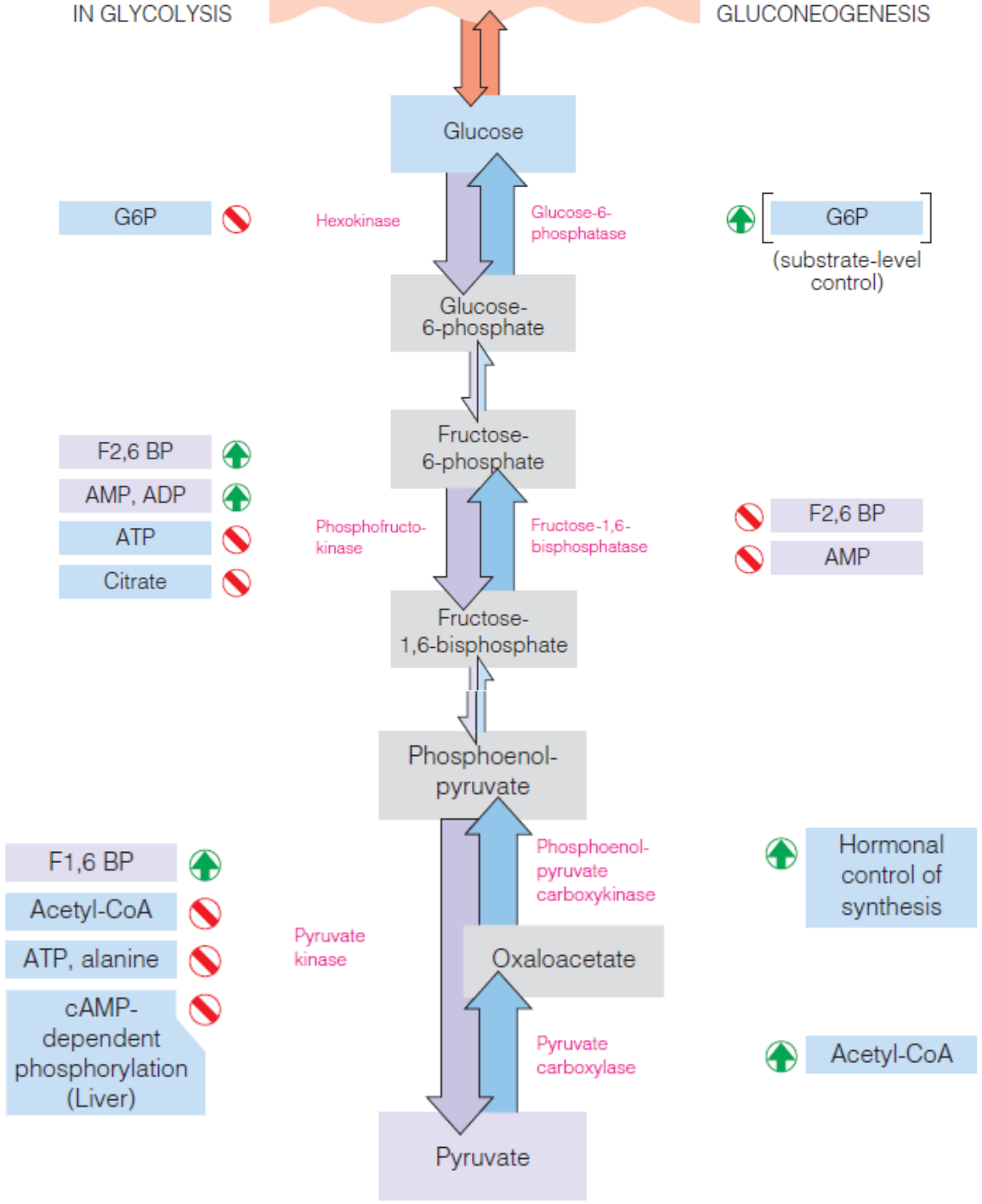
$$2\ \text{Pyruvate} + 4\text{ATP} + 2\text{GTP} + 2\text{NADH} + 2\text{H}^+ + 4\text{H}_2\text{O} \longrightarrow \text{glucose} + 4\text{ADP} + 2\text{GDP} + 6\text{P}_i + 2\text{NAD}^+$$

Outline of pathways for glucose synthesis from the major gluconeogenic precursors



# The Cori cycle






# Major control mechanisms affecting glycolysis and gluconeogenesis

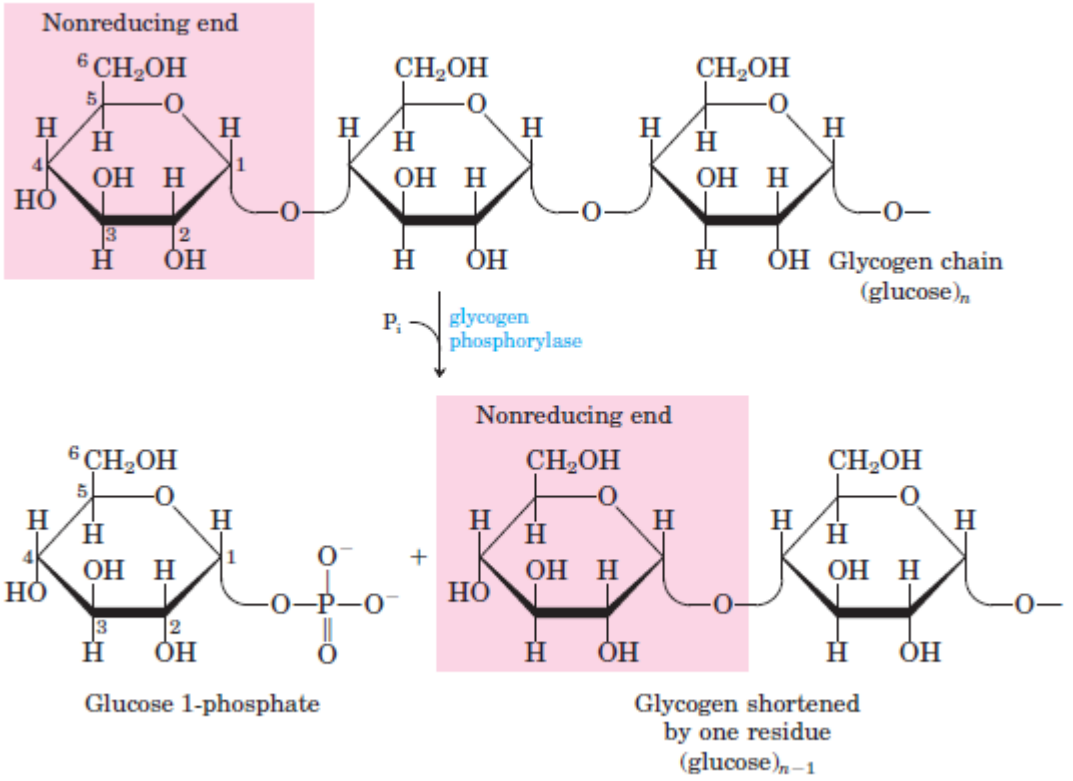
Key:

- Promotes glycolysis
- Promotes gluconeo-genesis
- Activation
- Inhibition

# Glycogen
## Introduction

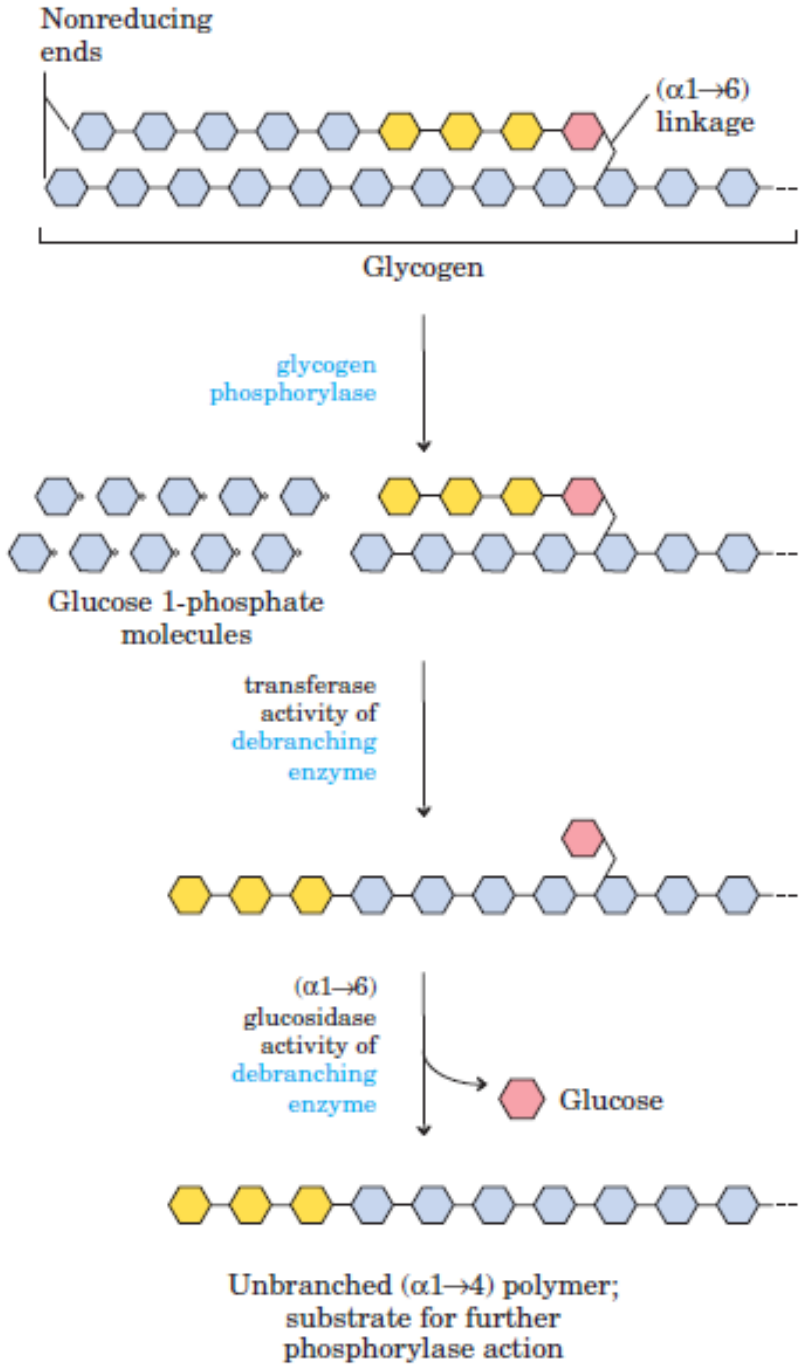
- In a wide range of organisms, excess glucose is converted to polymeric forms for storage—glycogen in vertebrates and many microorganisms, starch in plants
- In vertebrates, glycogen is found primarily in the liver and skeletal muscle; it may represent up to 10% of the weight of liver and 1% to 2% of the weight of muscle
- The glycogen in muscle is there to provide a quick source of energy for either aerobic or anaerobic metabolism. Muscle glycogen can be exhausted in less than an hour during vigorous activity. Liver glycogen serves as a reservoir of glucose for other tissues when dietary glucose is not available (between meals or during a fast)

# Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase

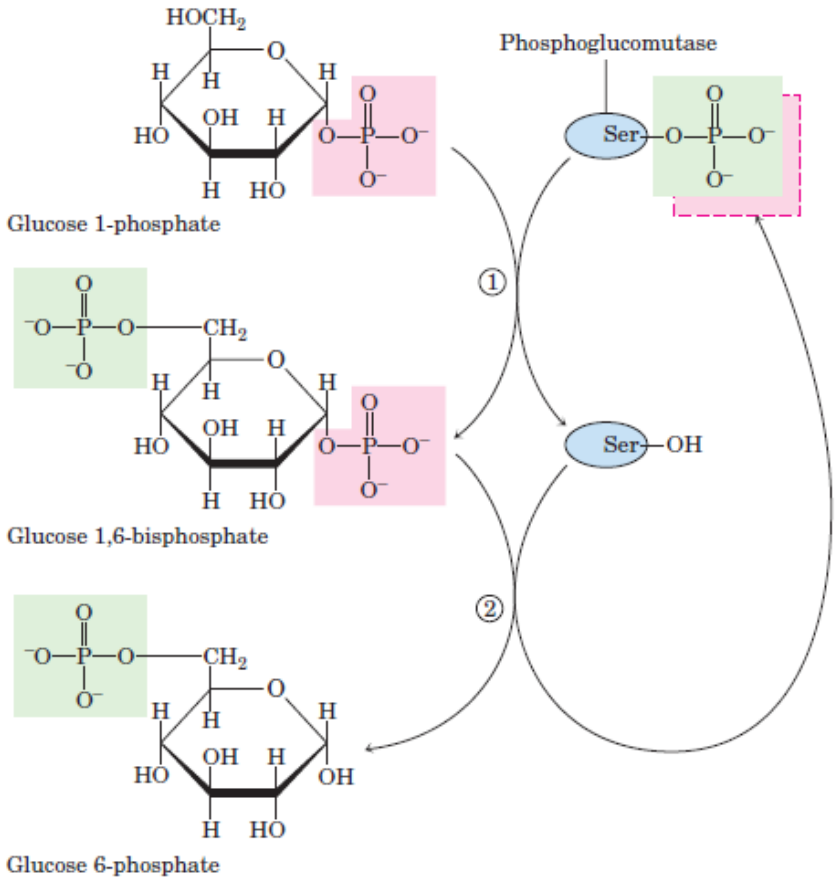



**Removal of a terminal glucose residue from the nonreducing end of a glycogen chain by glycogen phosphorylas**

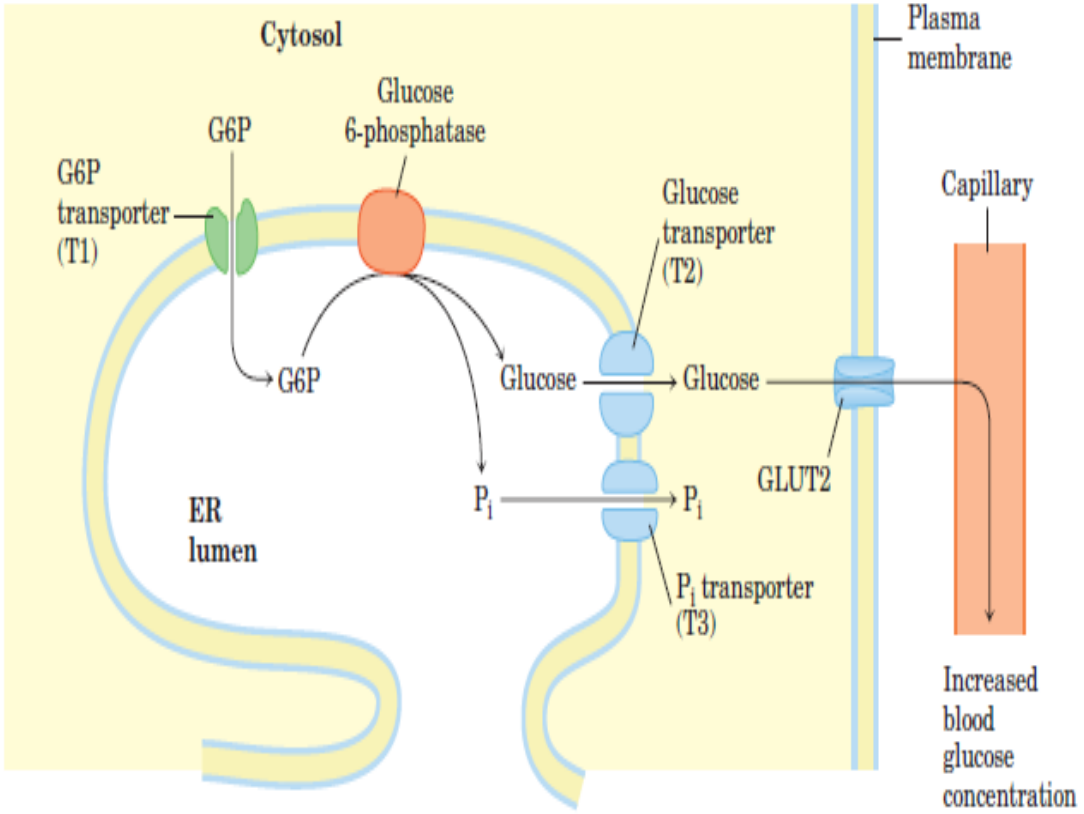
# Glycogen breakdown near an (alpha 1-6) branch point



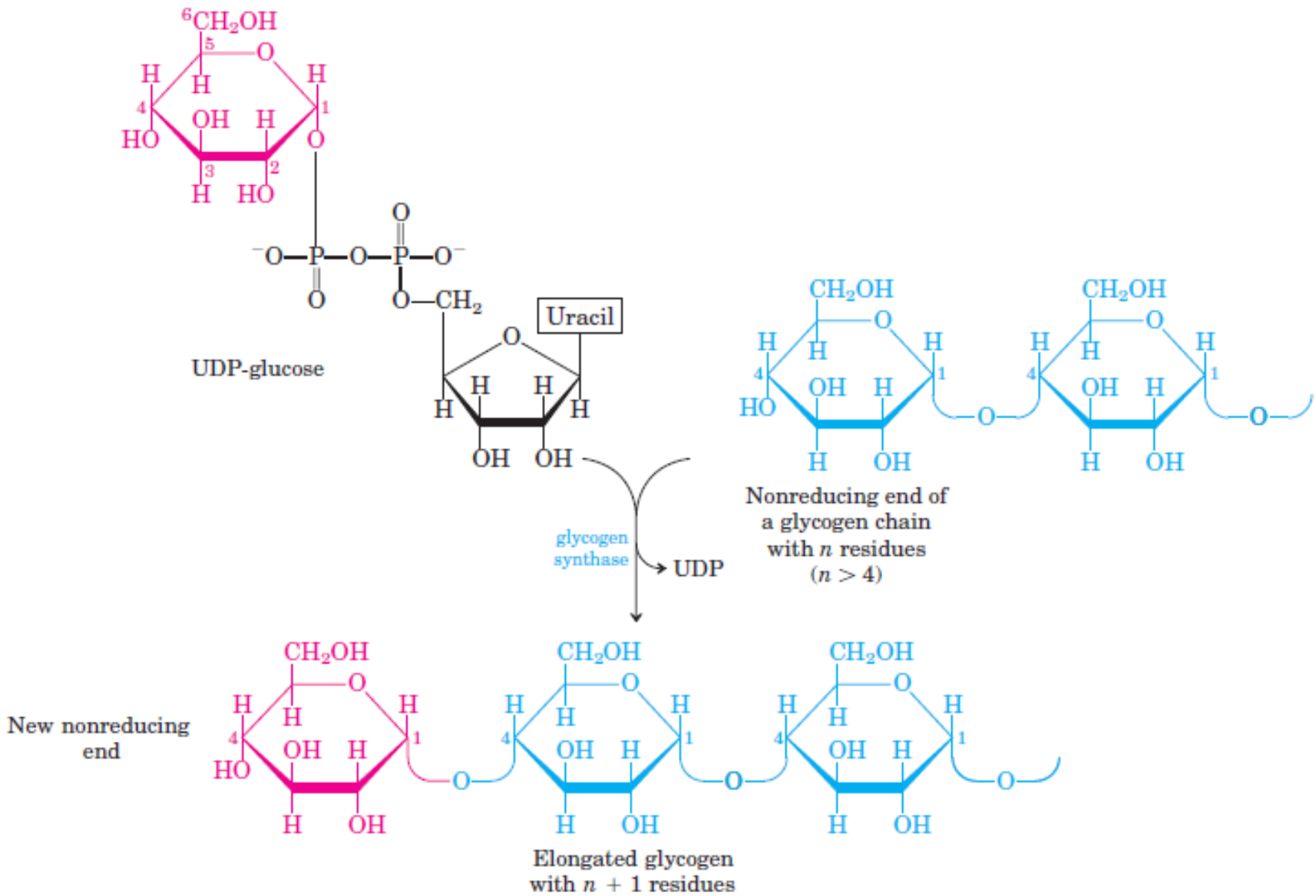
# Reaction catalyzed by phosphoglucomutase



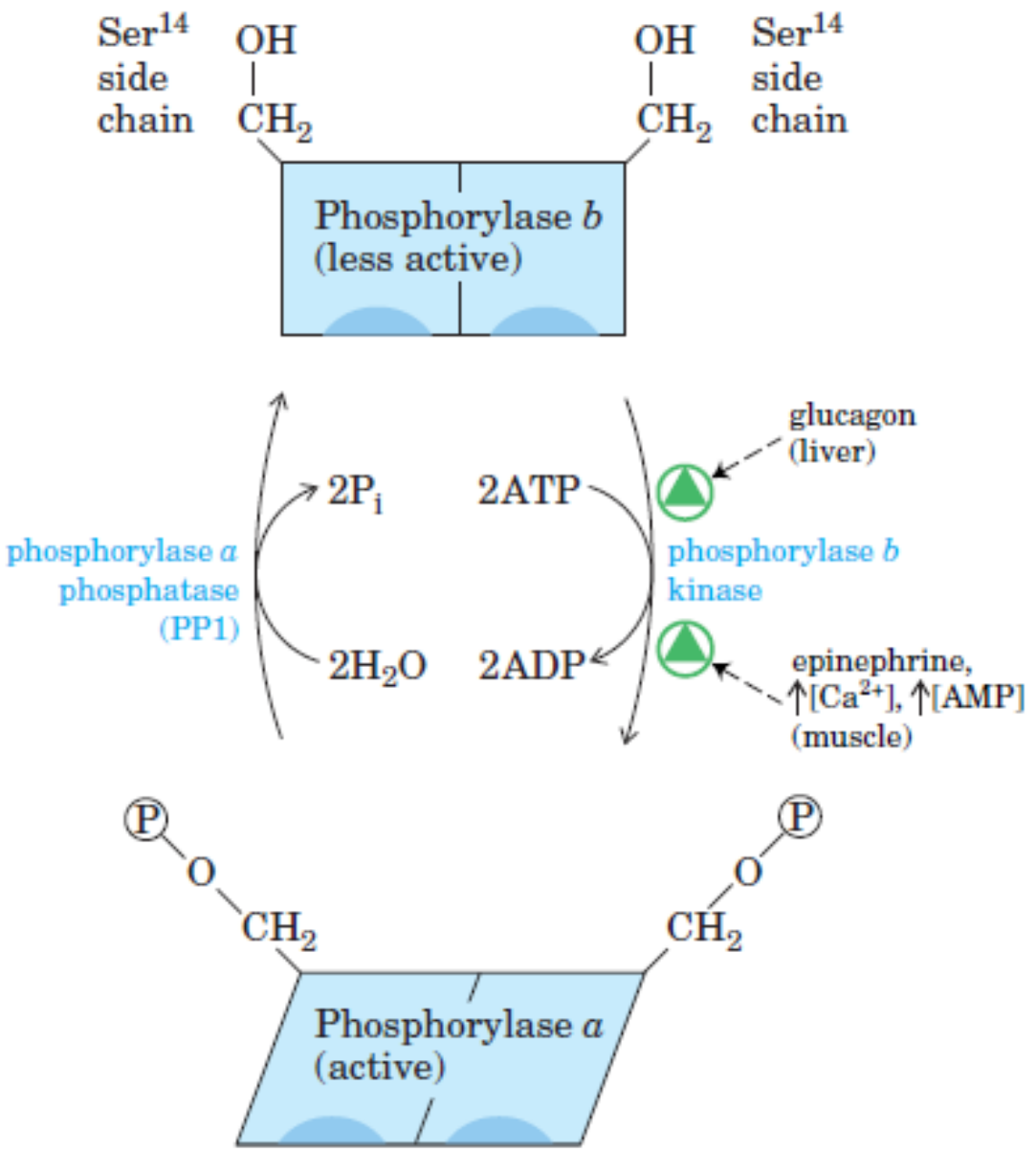

**Hydrolysis of glucose 6-phosphate by glucose 6- phosphatase of the ER.**



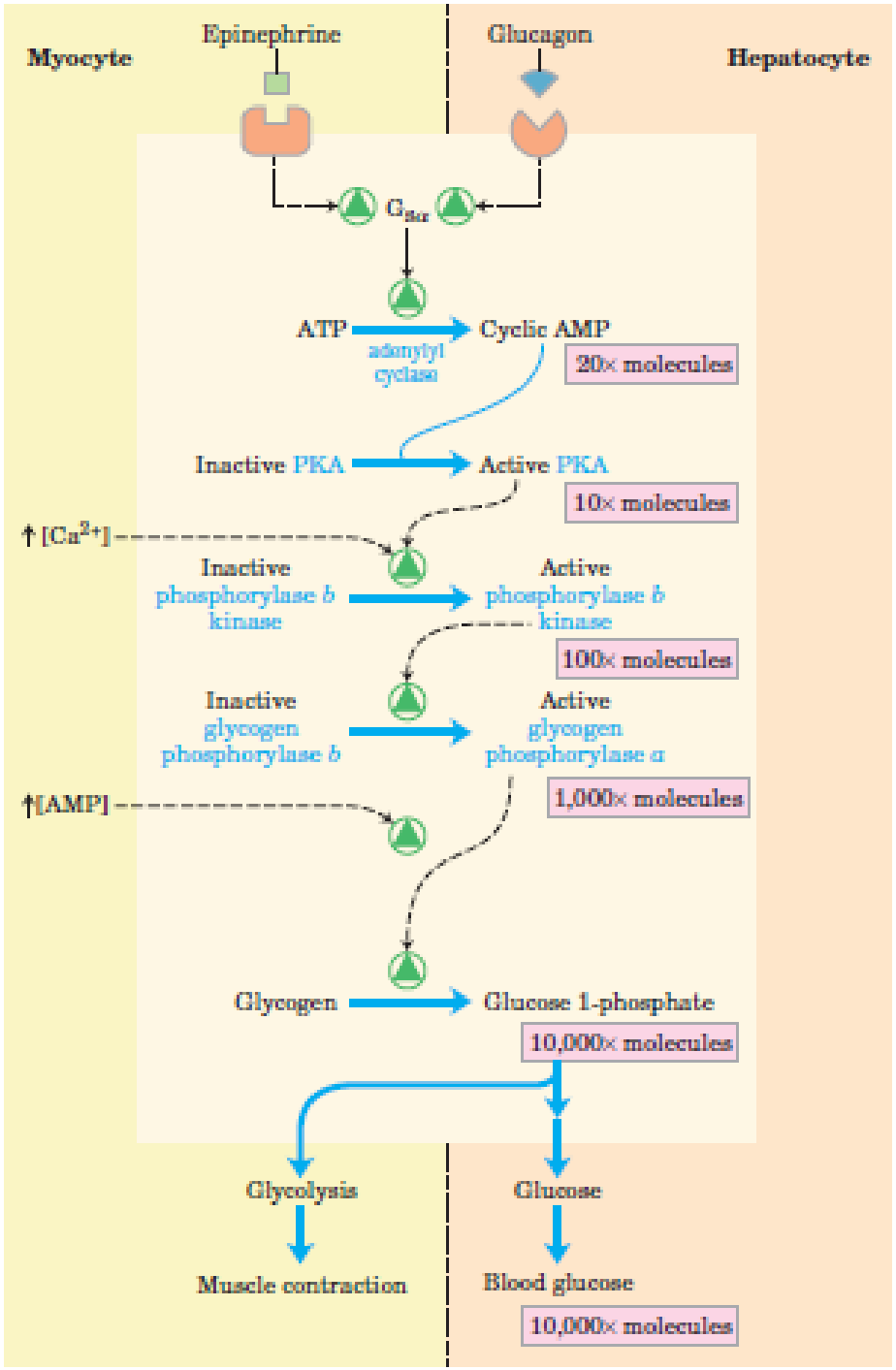
# Glycogen synthesis



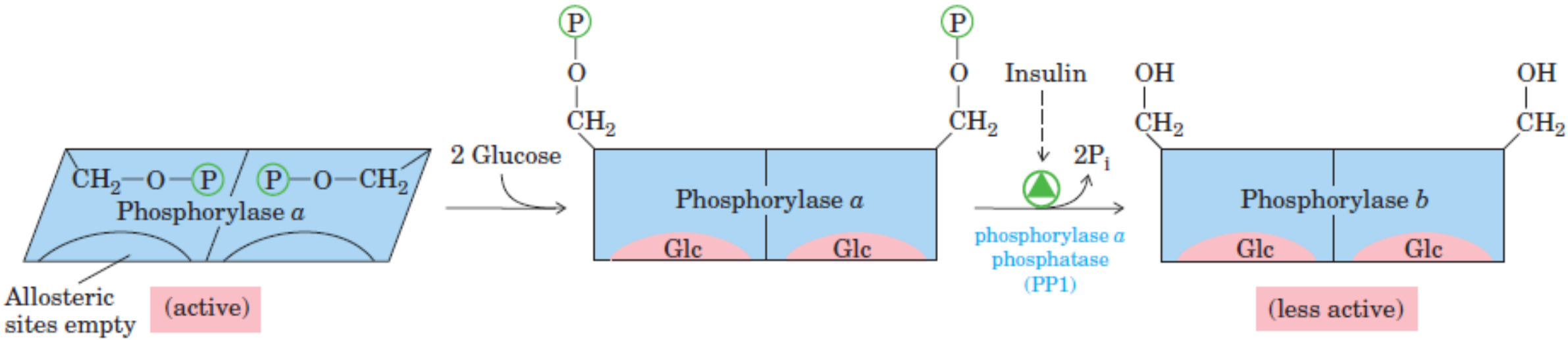
# Regulation of muscle glycogen phosphorylase by covalent modification

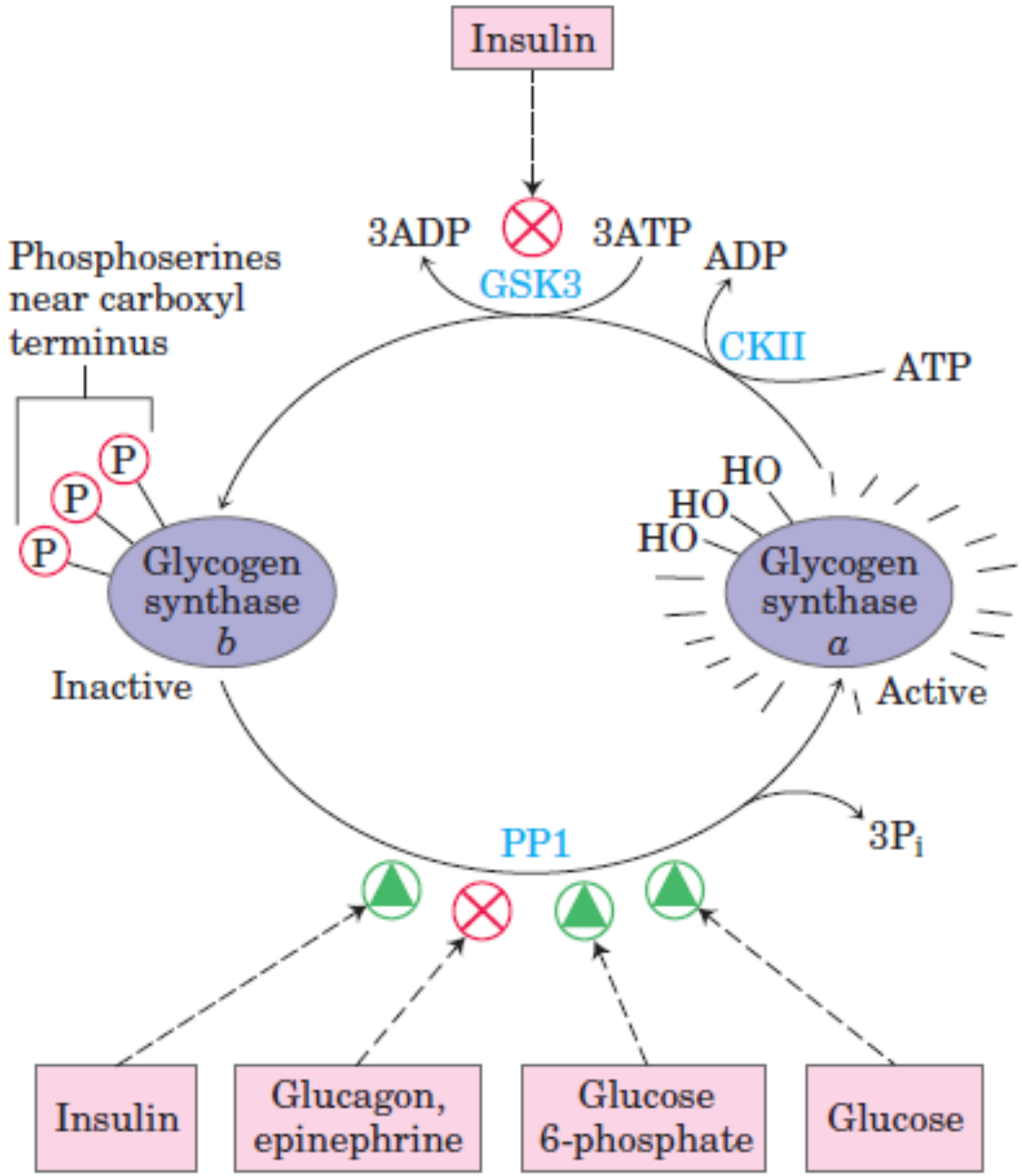


# Cascade mechanism of epinephrine and glucagon action



# Glycogen phosphorylase of liver as a glucose sensor



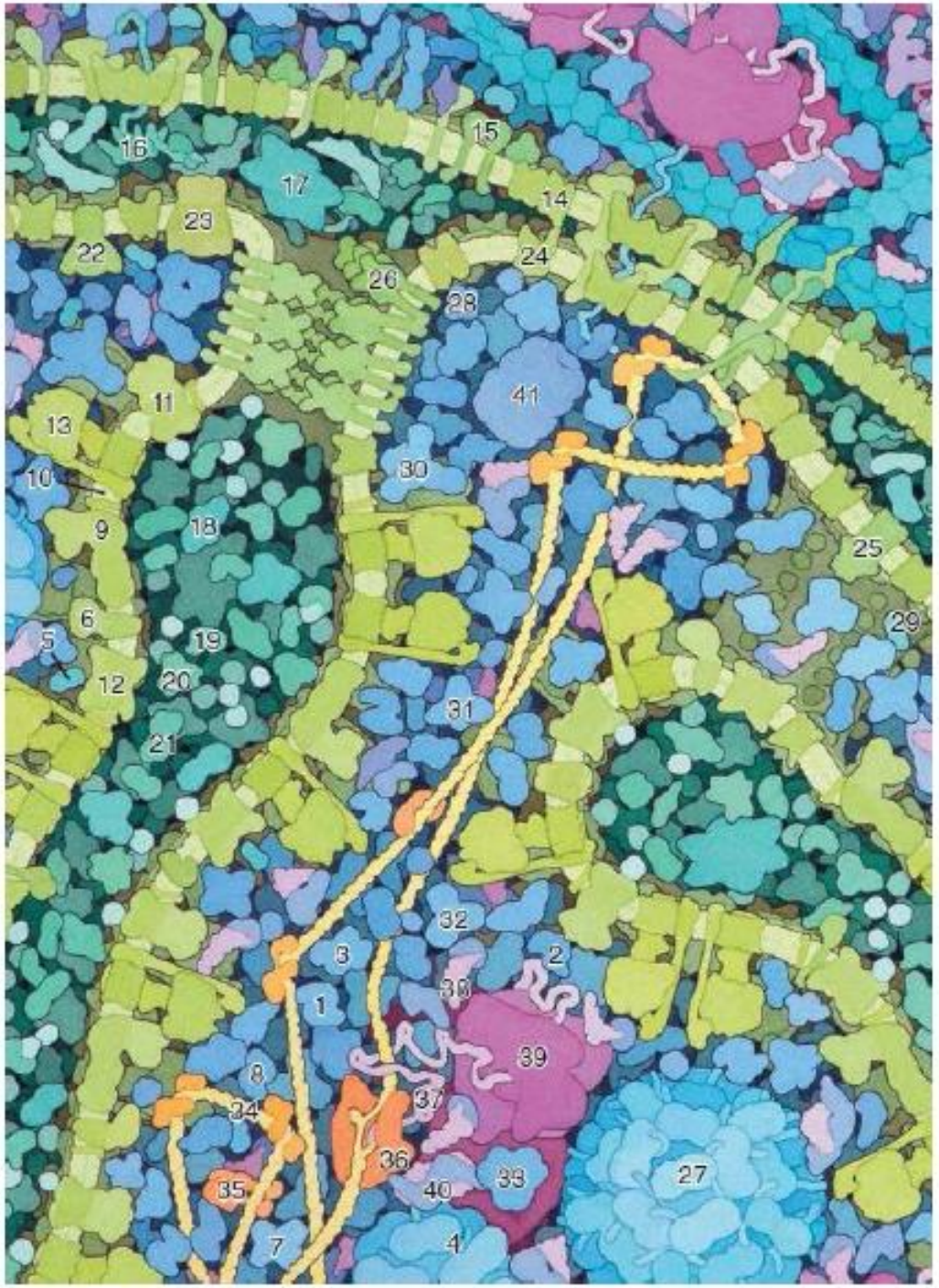

Insulin
3ADP
3ATP
GSK3
ADP
CKII
ATP
Phosphoserines near carboxyl terminus
P
P
P
Glycogen synthase b
Inactive
HO
HO
HO
Glycogen synthase a
Active
3Pi
PP1
Insulin
Glucagon, epinephrine
Glucose 6-phosphate
Glucose

# Lecture 4 Metabolism
# Kreb's Cycle

Dr. Bilal J M Aldahham

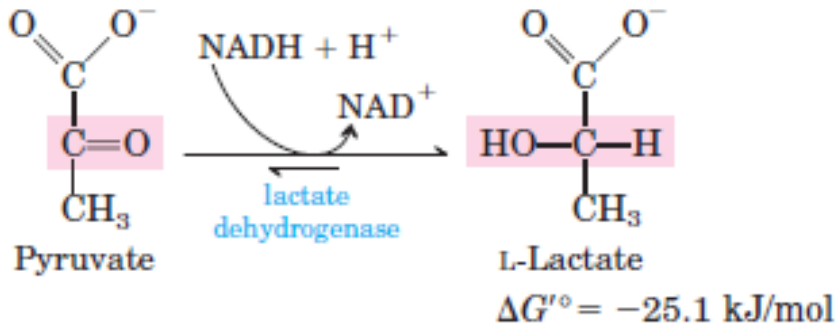
# Cross Section of a Mitochondrion

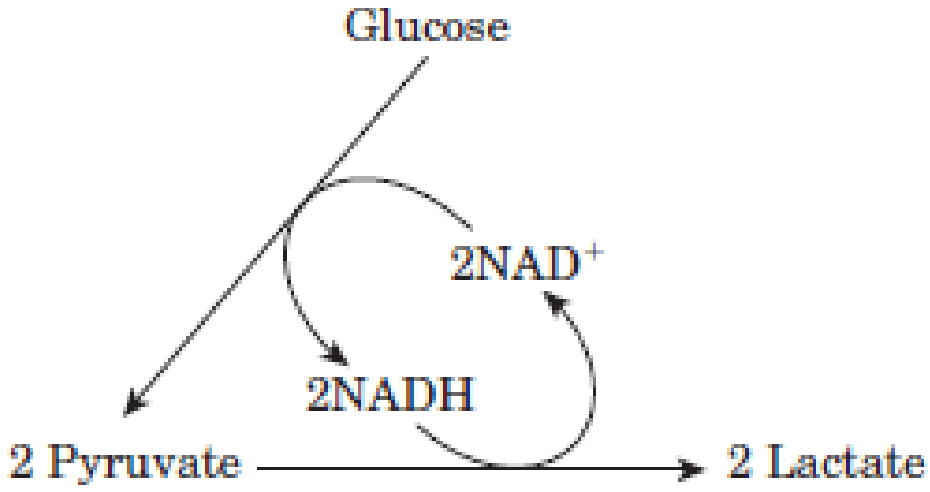
**This illustration, based on electron microscopy and X-ray crystallography**, shows a cross section of a mitochondrion in magnified molecular detail ($1 \times 10_6$). Each component is numbered. The citric acid cycle enzymes are (1) citrate synthase, (2) aconitase, (3) isocitrate dehydrogenase, (4) $\alpha$-ketoglutarate dehydrogenase, (5) succinyl CoA synthetase, (6) succinate dehydrogenase, (7) fumarase, and (8) malate dehydrogenase. The inner membrane electron transport chain components are (9) NADH dehydrogenase, (6) succinate dehydrogenase, (10) coenzyme Q, (11) cytochrome bc1 reductase, (12) cytochrome oxidase, and (13) ATP synthase. Note that for clarity the citric acid cycle enzymes and the electron transport system molecules



# Pyruvate Fate

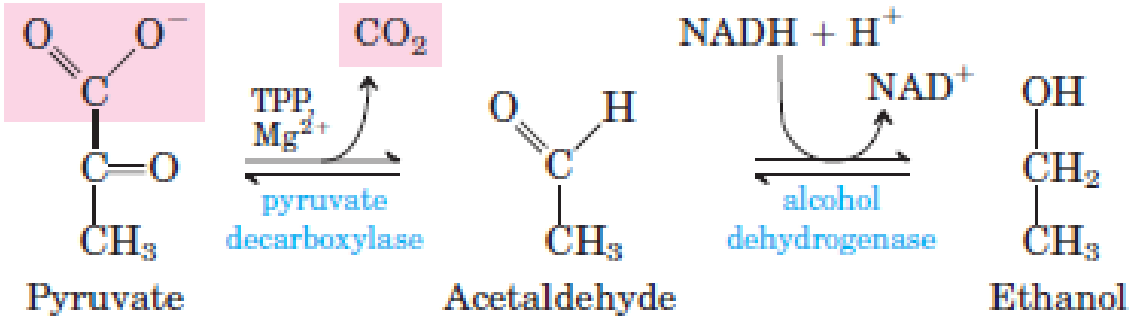
- **Fates of Pyruvate under Anaerobic Conditions: Fermentation**



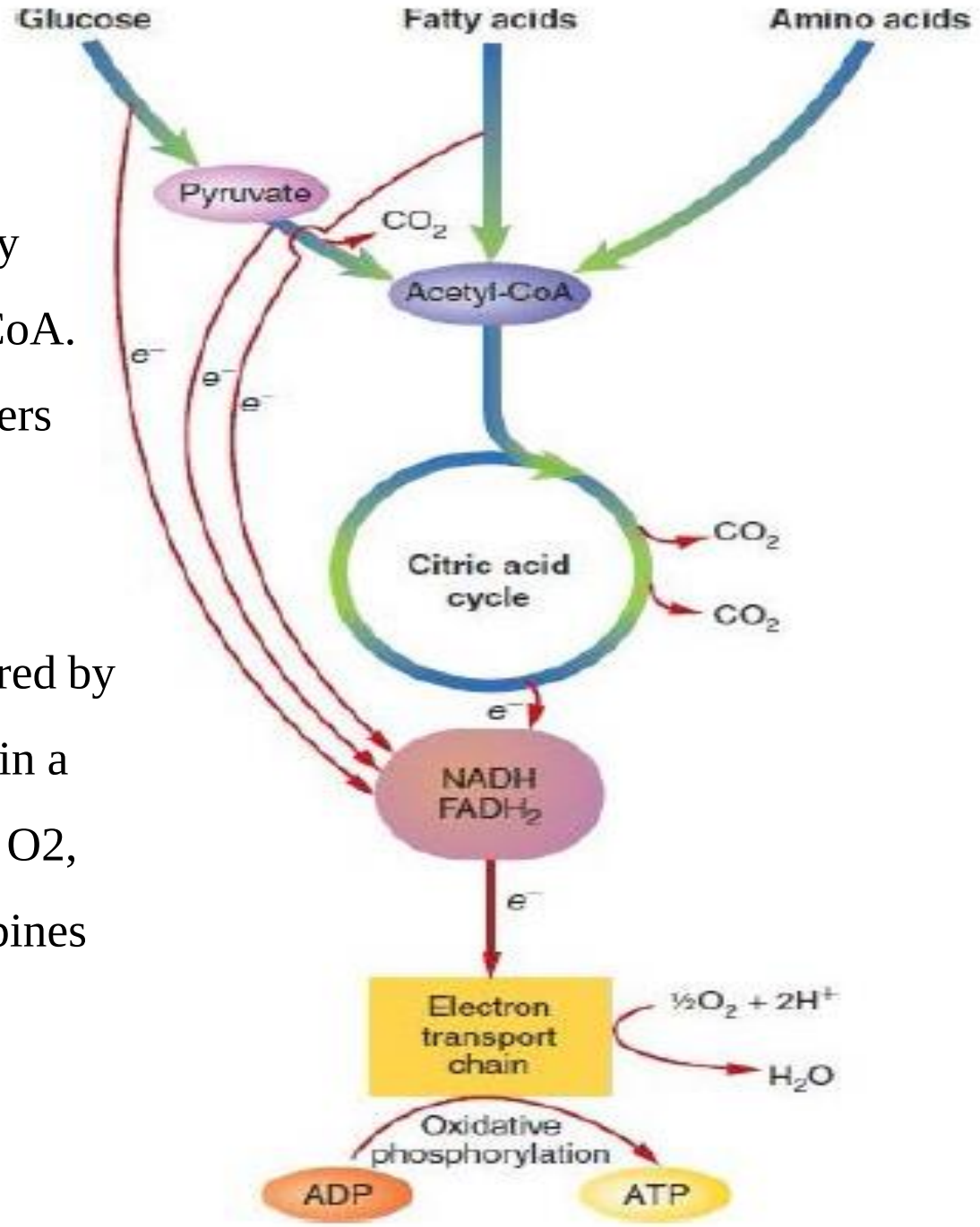
# Pyruvate Fate

- **Fates of Pyruvate under Anaerobic Conditions: Fermentation**



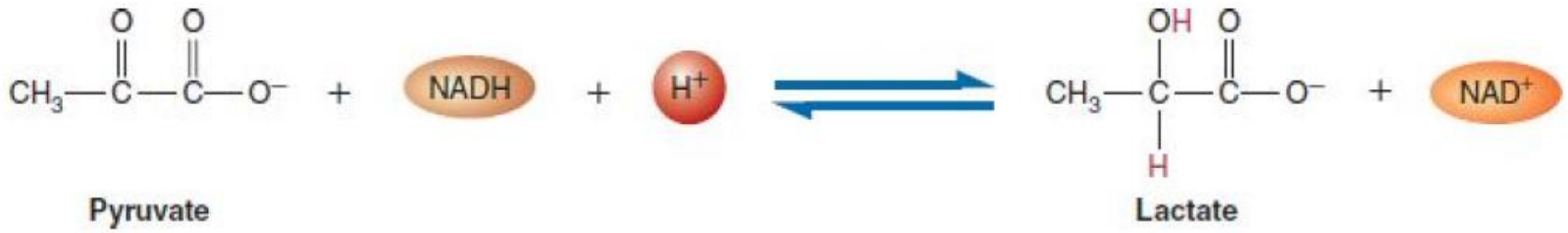
# Overview of Aerobic Metabolism

In aerobic metabolism, the nutrient molecules glucose, fatty acids, and some amino acids are degraded to form acetyl-CoA. Acetyl-CoA then enters the citric acid cycle. Electron carriers (NADH and FADH2) produced by glucose and fatty acid degradation and several citric acid cycle reactions donate electrons (*e*–) to the electron transport chain. Energy captured by the electron transport chain is then used to synthesize ATP in a process referred to as oxidative phosphorylation. Note that O2, the terminal electron acceptor in aerobic metabolism, combines with protons to form water molecules

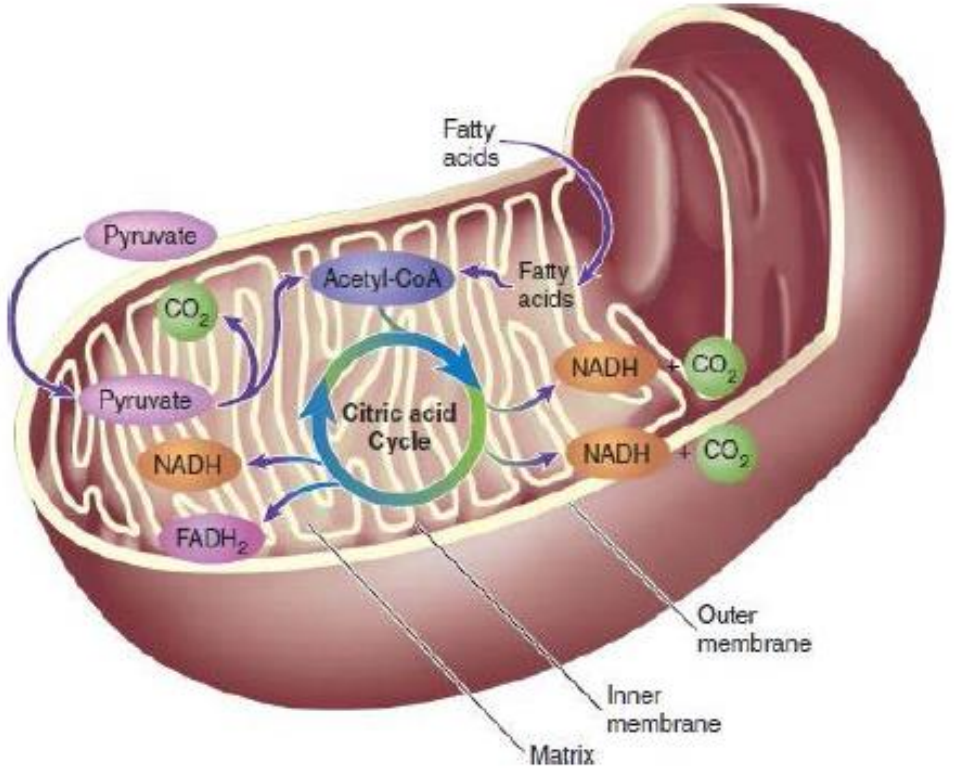


# Aerobic Metabolism in the Mitochondrion

## OXIDATION-REDUCTION REACTIONS




In this redox reaction, a hydride ion ($H:^-$) is transferred from NADH to pyruvate, and the product is protonated from the surrounding medium to form lactate.

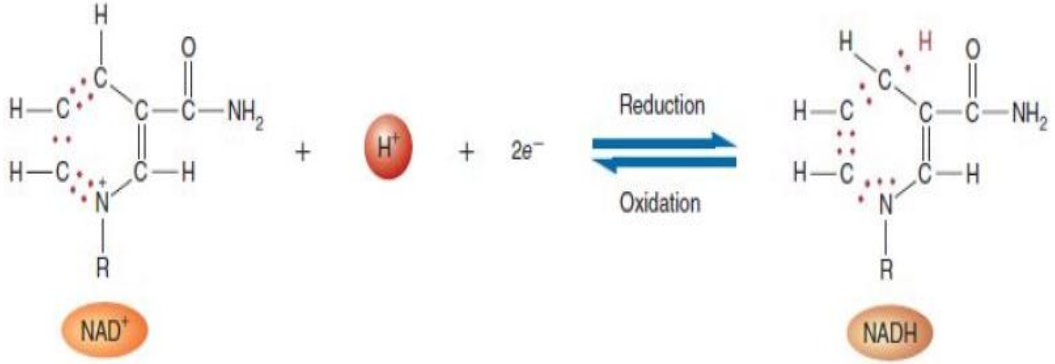


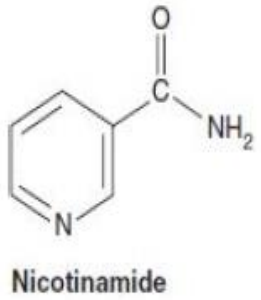
# Standard Reduction Potentials

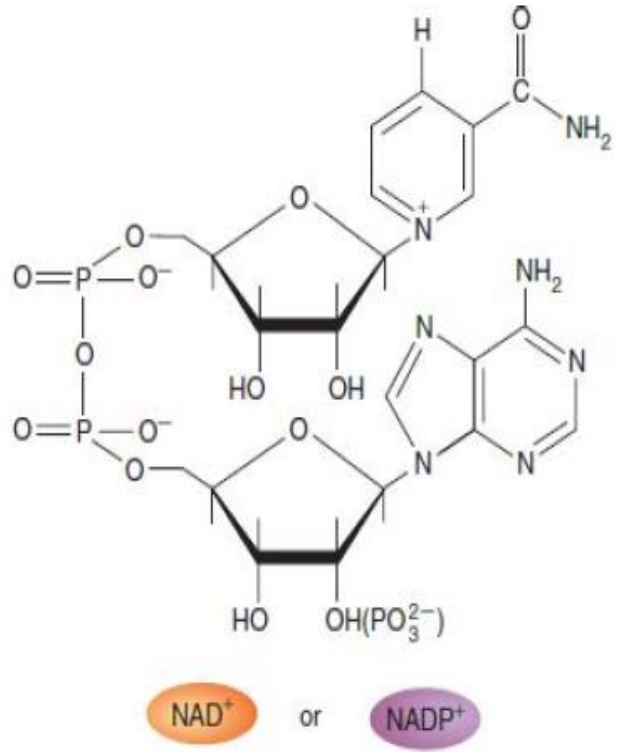
| Redox Half-Reaction | Standard Reduction Potentials ($E°'$) (V) |
|---|---|
| $2H^+ + 2e^- \rightarrow H_2$ | −0.42 |
| α-Ketoglutarate + $CO_2$ + $2H^+ + 2e^- \rightarrow$ isocitrate | −0.38 |
| $NADP^+ + H^+ + 2e^- \rightarrow$ NADPH | −0.324 |
| $FAD + 2H^+ + 2e^- \rightarrow FADH_2$ | −0.22 |
| Acetaldehyde + $2H^+ + 2e^- \rightarrow$ ethanol | −0.20 |
| Pyruvate + $2H^+ + 2e^- \rightarrow$ lactate | −0.19 |
| $^1/_2O_2 + 2H^+ + 2e^- \rightarrow H_2O$ | +0.82 |

# Redox Coenzymes

- **NICOTINIC ACID** There are two coenzyme forms of nicotinic acid: **nicotinamide adenine dinucleotide (NAD)** and **nicotinamide adenine dinucleotide phosphate (NADP)**. These coenzymes occur in oxidized forms (NAD+ and NADP+) and reduced forms (NADH and NADPH).

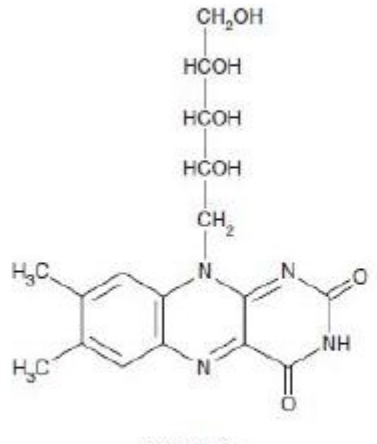


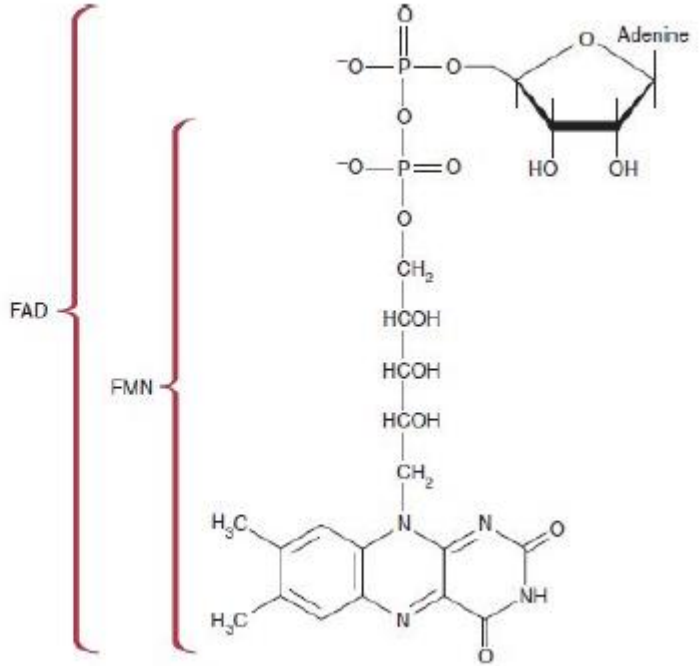



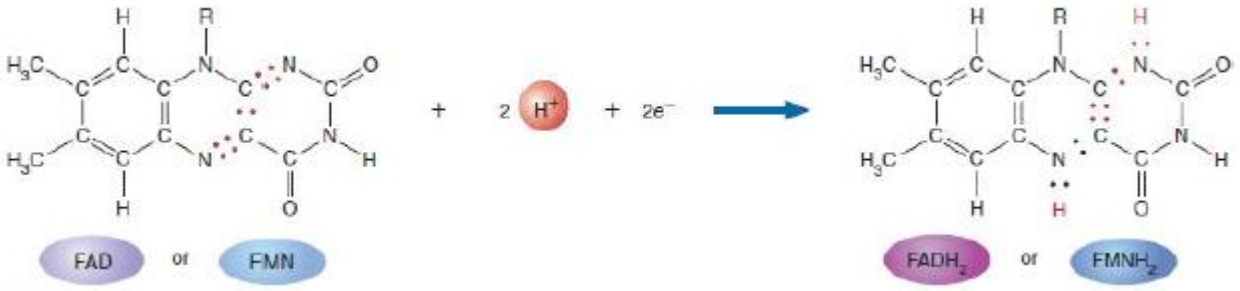



# Redox Coenzymes

- **RIBOFLAVIN** Riboflavin (vitamin B2) is a component of two coenzymes: **flavin mononucleotide (FMN)** and **flavin adenine dinucleotide (FAD)**



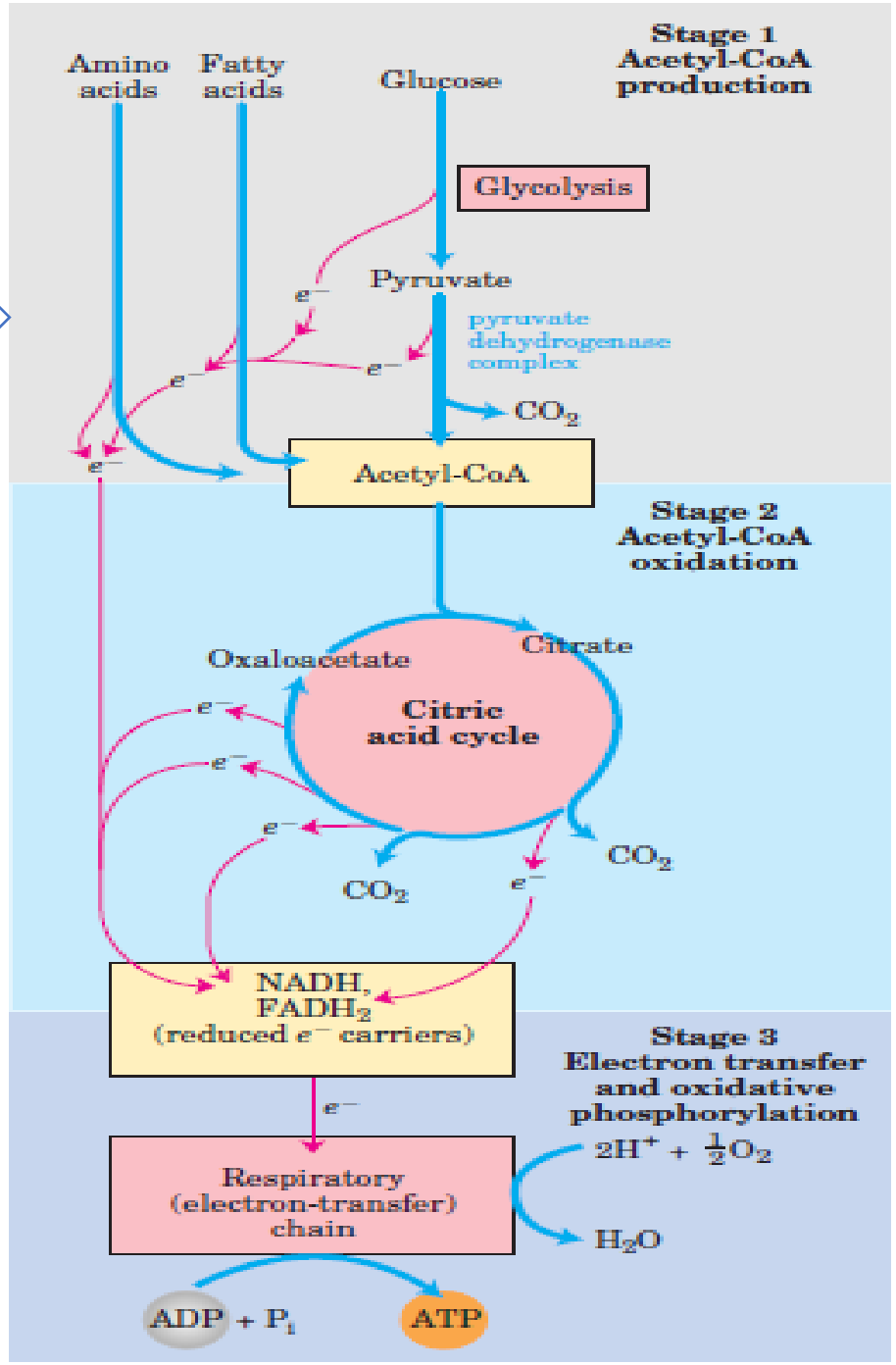
# cellular respiration

- Why it is called Respiration?
- Cellular respiration occurs in:
- "three major stages"

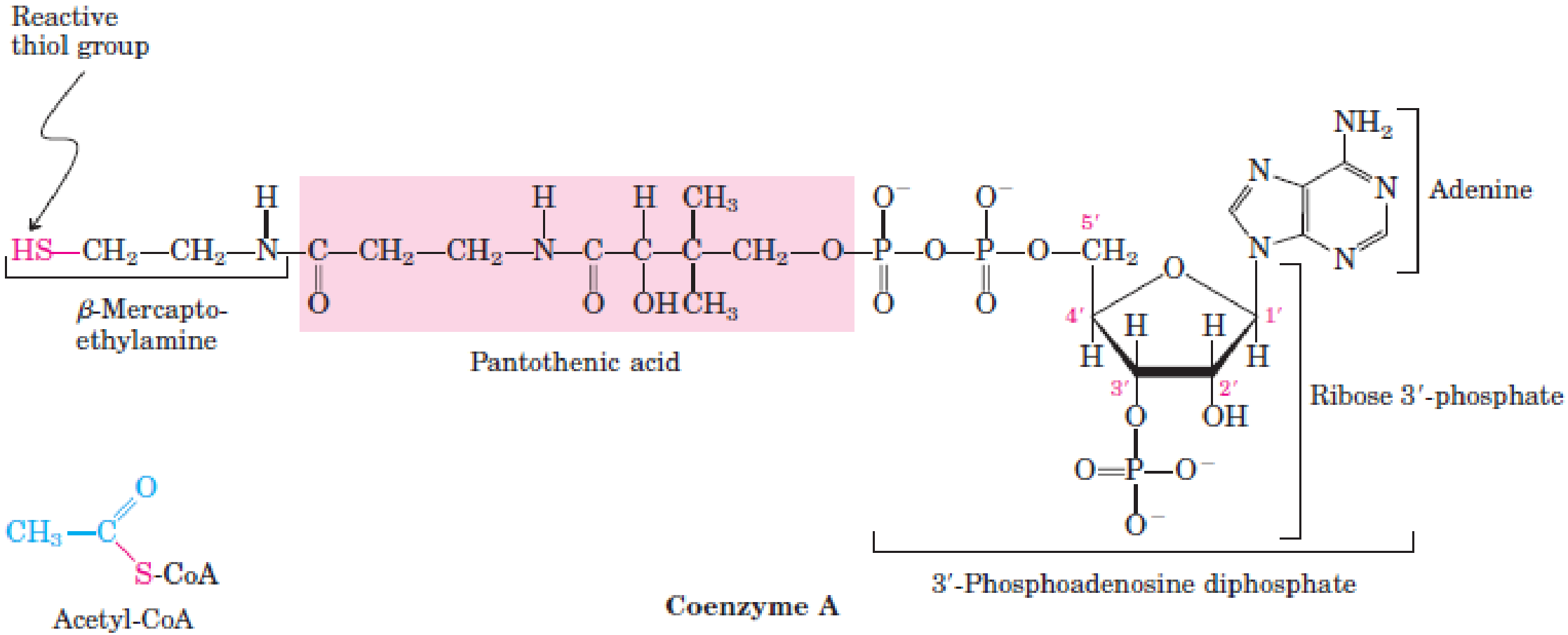
In the first, organic fuel molecules—glucose, fatty acids, and some amino acids—are oxidized to yield two-carbon fragments in the form of the acetyl group of acetyl-coenzyme A (acetyl-CoA).

**In the second stage, the acetyl groups are fed into the citric acid cycle, which enzymatically oxidizes them to $CO_2$; the energy released is conserved in the reduced electron carriers NADH and $FADH_2$.**

In the third stage of respiration, these reduced coenzymes are themselves oxidized, giving up protons (H) and electrons. The electrons are transferred to $O_2$—the final electron acceptor—via a chain of electron-carrying molecules known as the respiratory chain

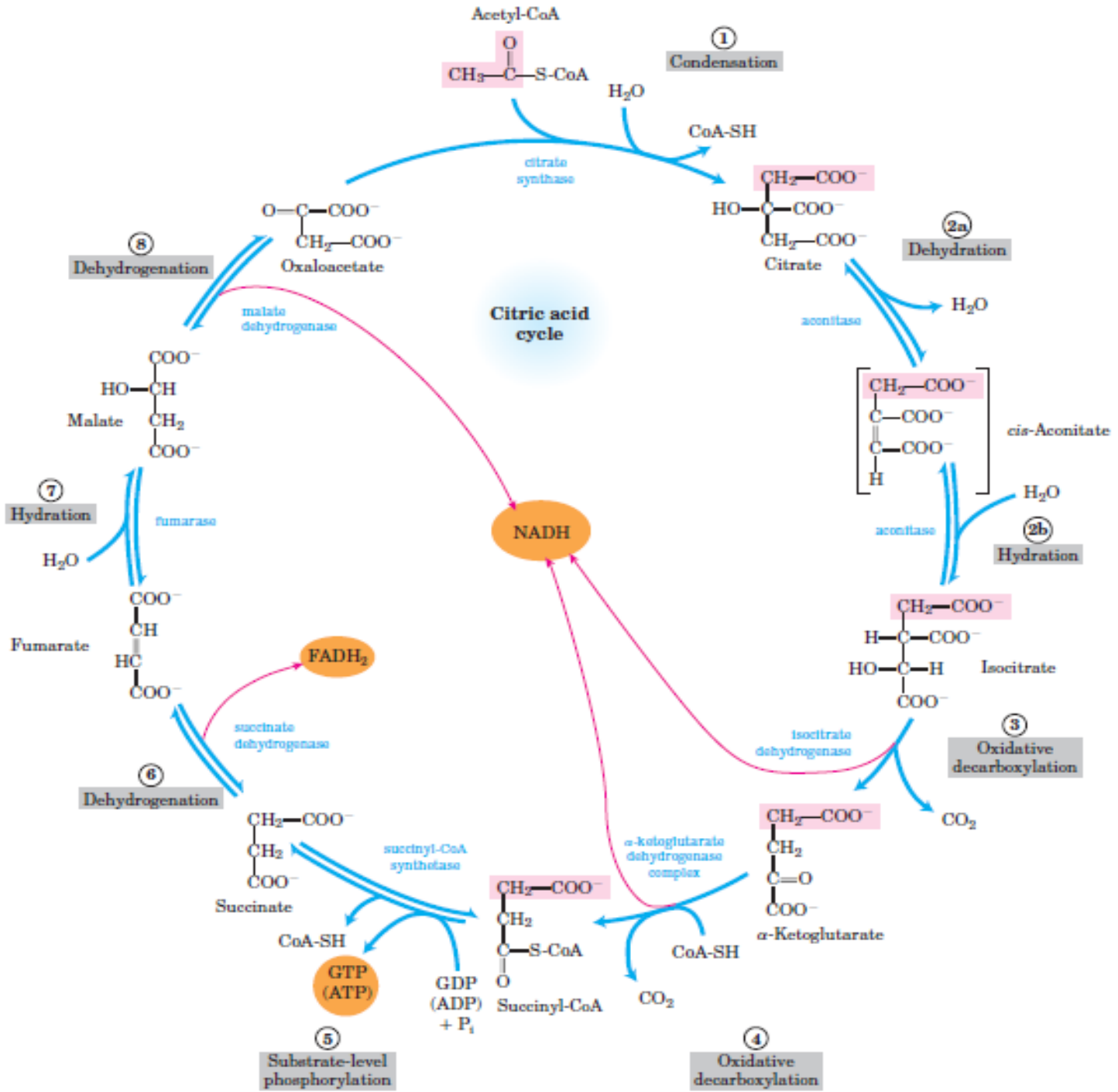


# Coenzyme A and Acetyl-CoA

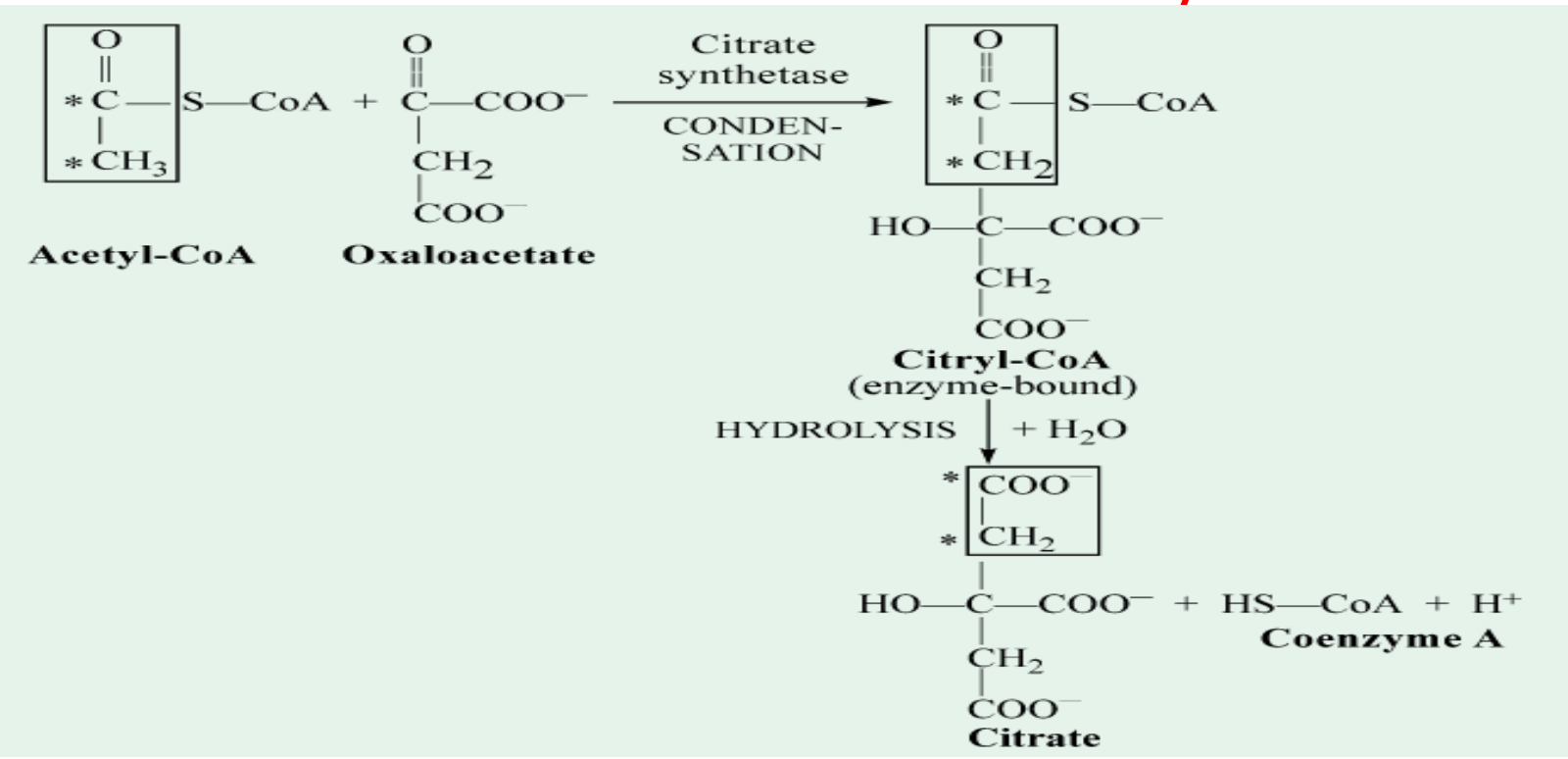


# Reactions of the Citric Acid Cycle

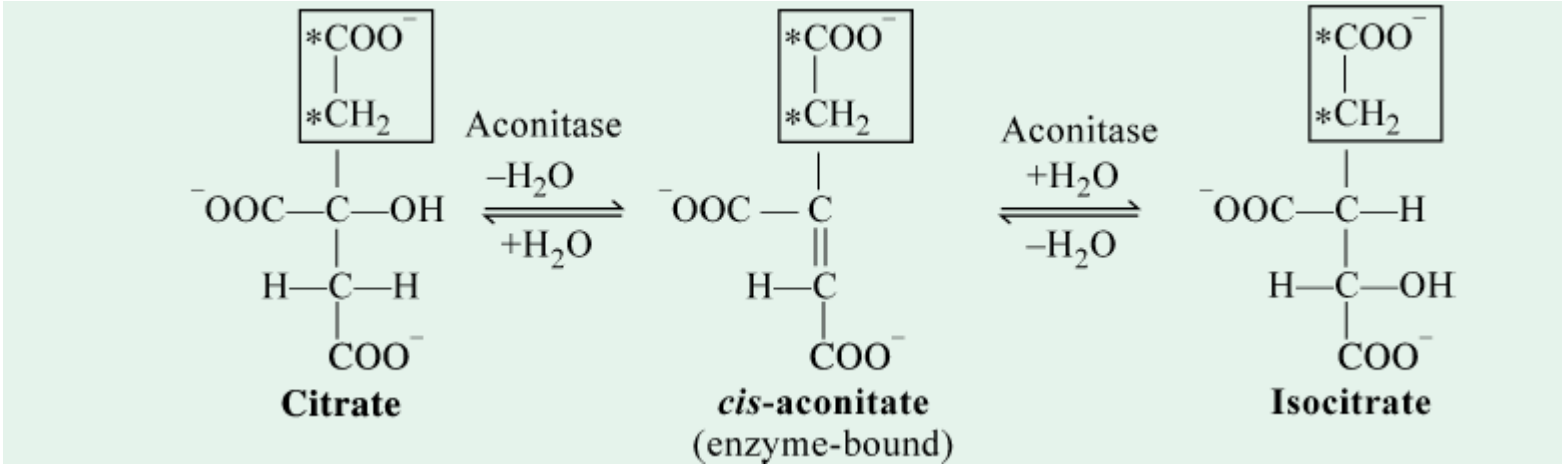
Hans Krebs, 1900–1981



# Reactions of Citric acid cycle



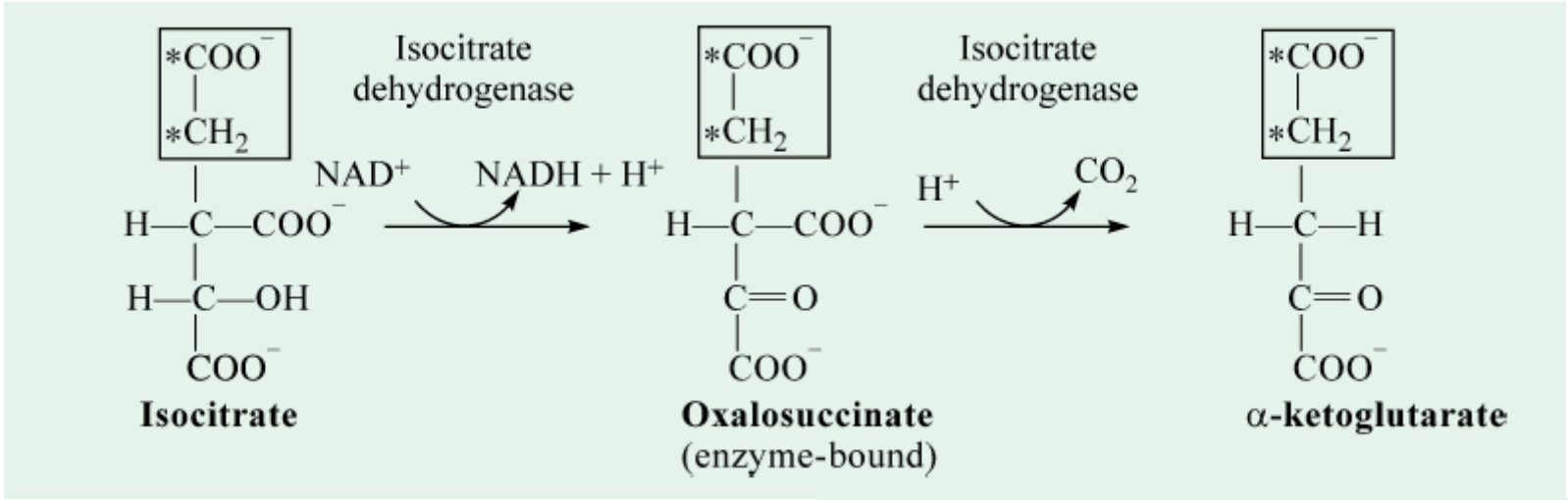

1. The citric acid cycle begins with the condensation of acetyl-CoA with oxaloacetate to form citrate



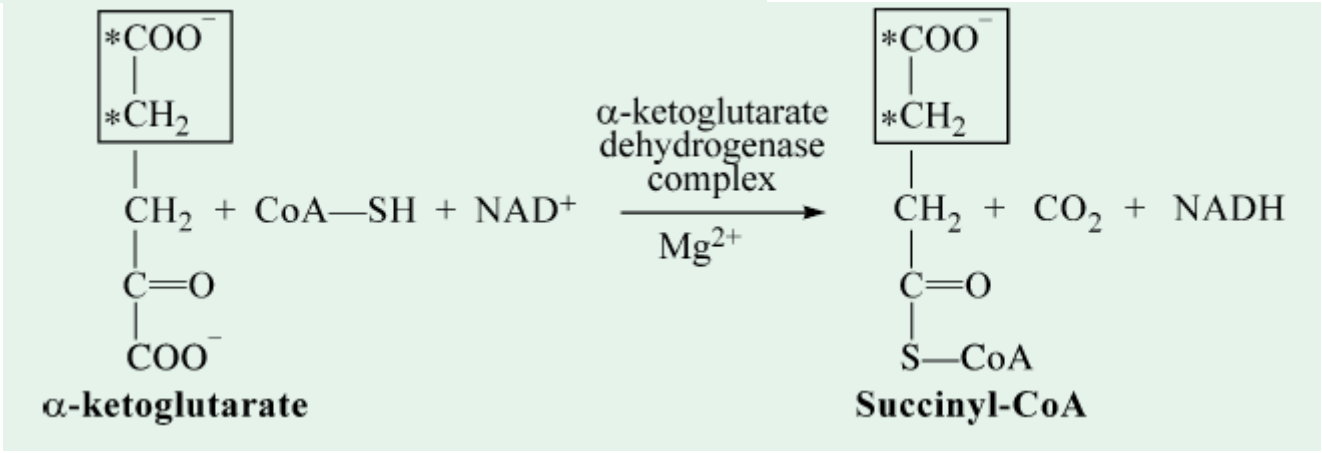

2. Citrate is isomerized to form a secondary alcohol that can be easily oxidized

# Reactions of Citric acid cycle

**3. Isocitrate is oxidized to form *α*-ketoglutarate and $CO_2$**

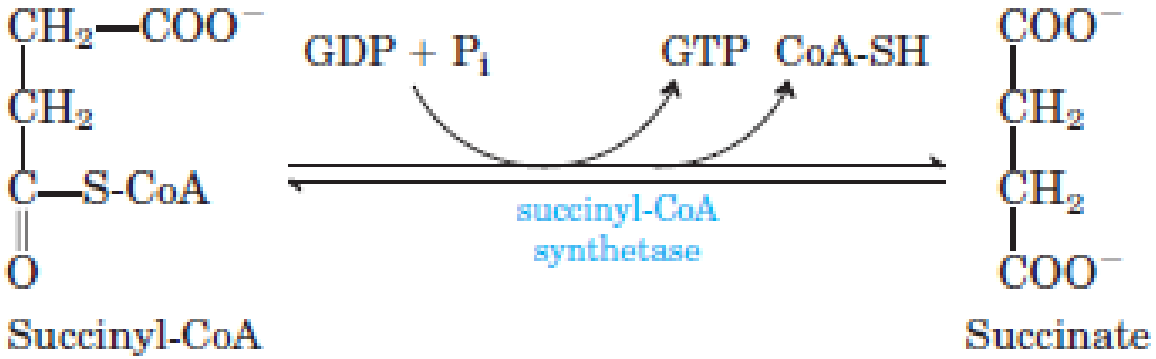



***4. α*-Ketoglutarate is oxidized to form a second molecule each of NADH and $CO_2$**



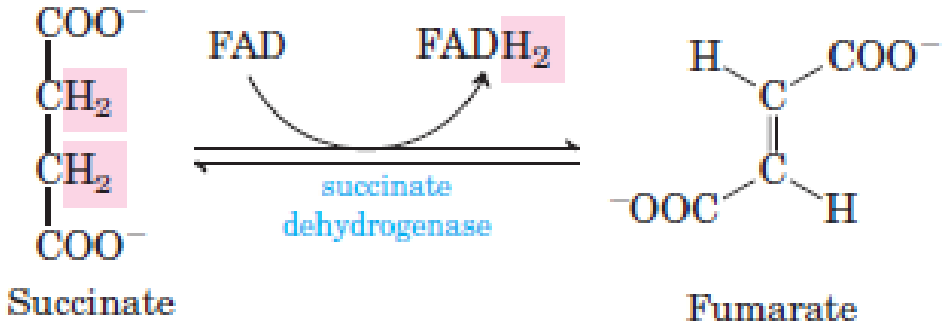
# Reactions of Citric acid cycle

**5. The cleavage of succinyl-CoA is coupled to a substrate-level phosphorylation**



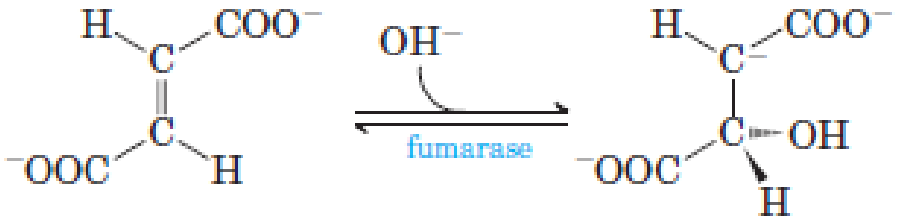

Succinyl-CoA Succinate

**6. The four-carbon molecule succinate is oxidized to form fumarate and $FADH_2$**




Succinate Fumarate

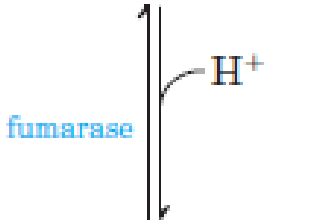
# Reactions of Citric acid cycle

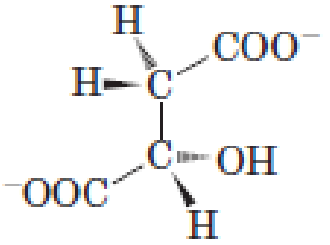



Fumarate

Carbanion transition state

## 7. Fumarate is hydrated

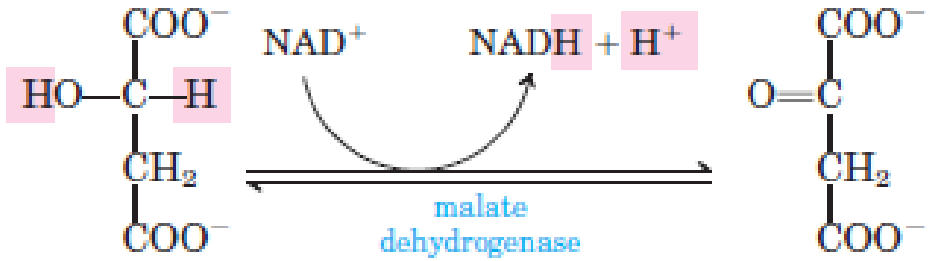



Malate

**8. Malate is oxidized to form OAA and a third NADH**

Finally, OAA is regenerated with
the oxidation of L-malate by malate dehydrogenase

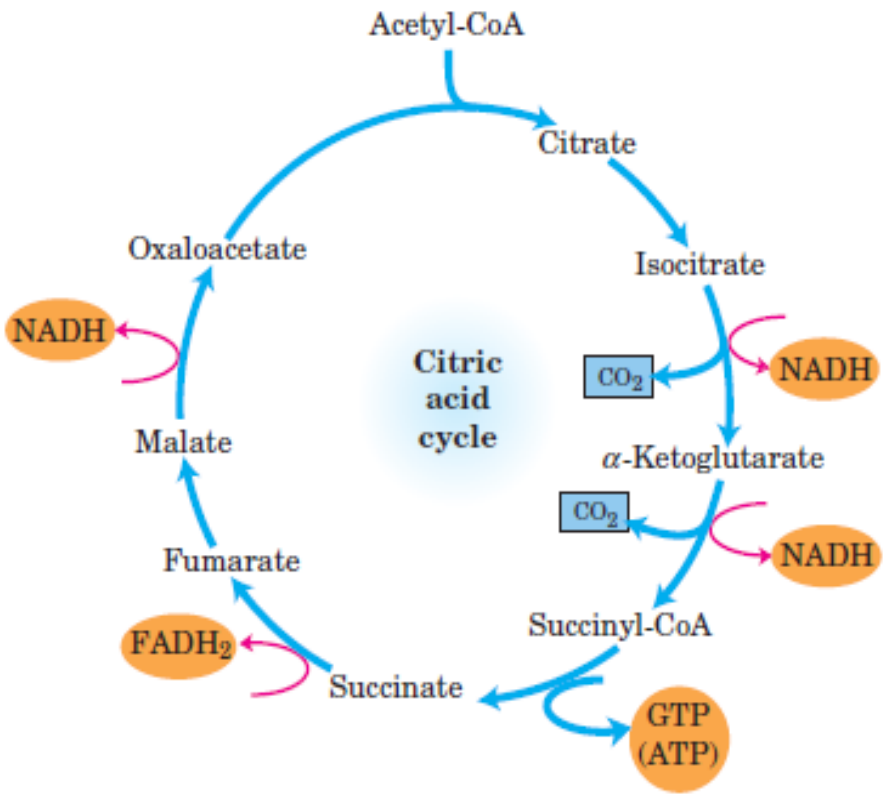



L-Malate

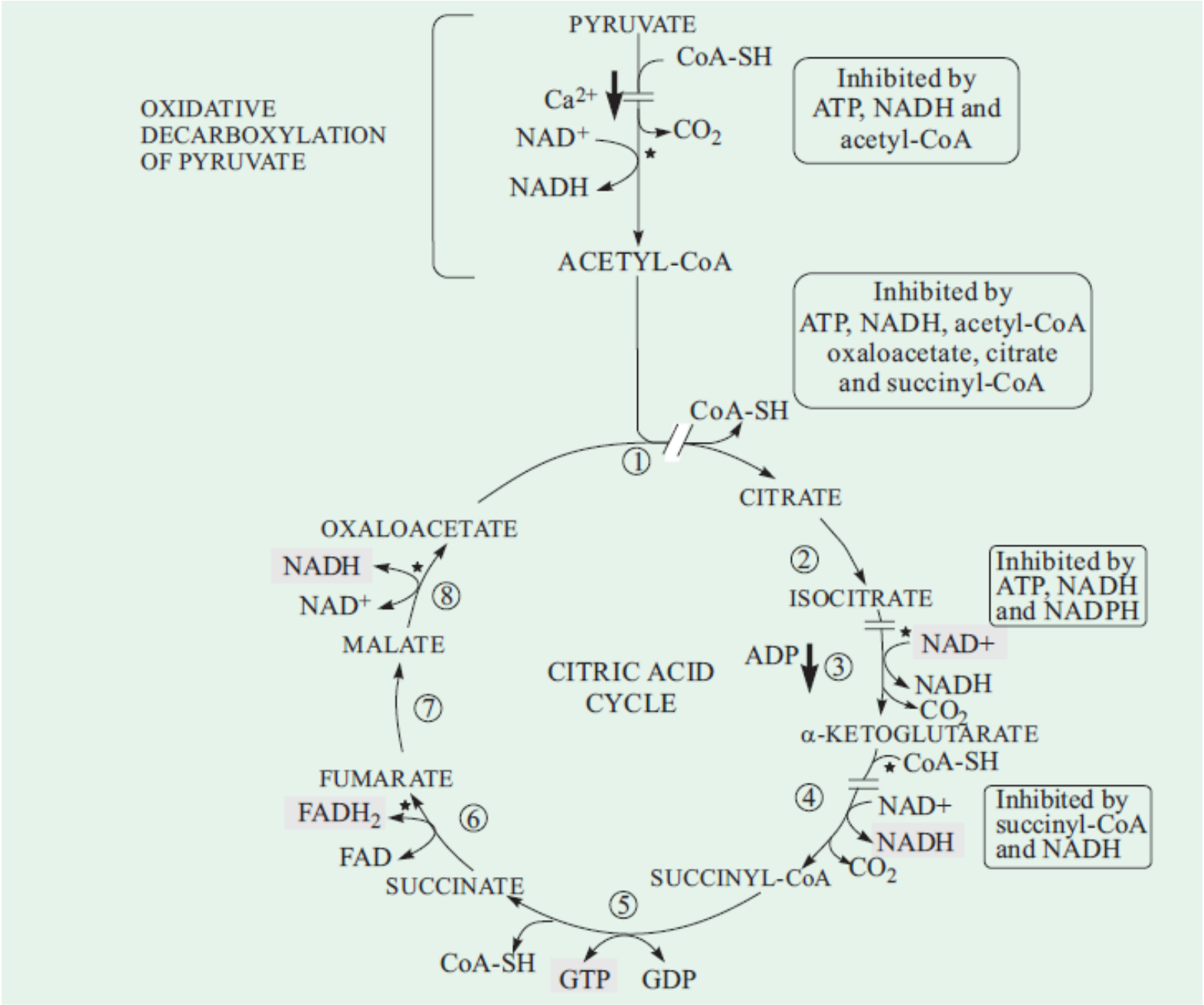
Oxaloacetate

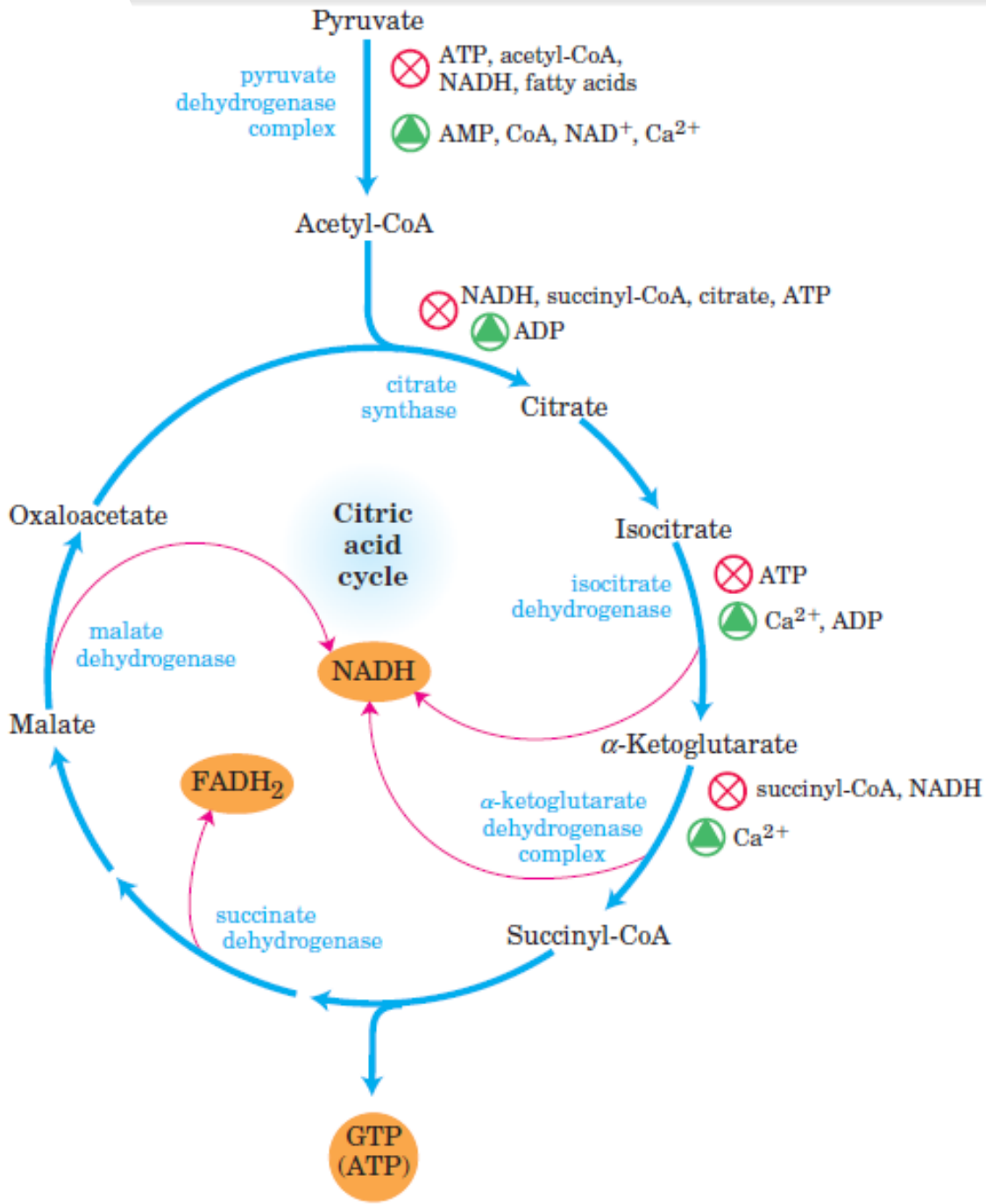
# Energy yield of the citric acid cycle

| *Step No.* | *Reaction* | *Method of ATP Formation* | *ATP Yield Per Mole* |
|---|---|---|---|
| 3 | Isocitrate → α-ketoglutarate + $CO_2$ | Respiratory chain oxidation of NADH | 3 |
| 4 | α-ketoglutarate → Succinyl-CoA + $CO_2$ | Respiratory chain oxidation of NADH | 3 |
| 5 | Succinyl-CoA + ADP + P*i* → Succinate + ATP | Oxidation at substrate level | 1 |
| 6 | Succinate → Fumarate | Respiratory chain oxidation of $FADH_2$ | 2 |
| 8 | Malate → Oxaloacetate | Respiratory chain oxidation of NADH | 3 |
| | | Total gain of ATP = 12 | |



# Control of the oxidative decarboxylation of pyruvate and the citric acid cycle




Pyruvate
pyruvate dehydrogenase complex
ATP, acetyl-CoA, NADH, fatty acids
AMP, CoA, NAD+, Ca2+
Acetyl-CoA
NADH, succinyl-CoA, citrate, ATP
ADP
citrate synthase
Citrate
Isocitrate
ATP
Ca2+, ADP
isocitrate dehydrogenase
α-Ketoglutarate
succinyl-CoA, NADH
Ca2+
α-ketoglutarate dehydrogenase complex
Succinyl-CoA
succinate dehydrogenase
FADH2
Malate
malate dehydrogenase
NADH
Oxaloacetate
Citric acid cycle
GTP (ATP)

# Regulation of metabolite flow from the PDH complex through the citric acid cycle

The PDH complex is allosterically inhibited when [ATP]/[ADP], [NADH]/[NAD], and [acetyl-CoA]/[CoA] ratios are high, indicating an energy-sufficient metabolic state. When these ratios decrease, allosteric activation of pyruvate oxidation results. The rate of flow through the citric acid cycle can be limited by the availability of the citrate synthase substrates, oxaloacetate and acetyl-CoA, or of NAD, which is depleted by its conversion to NADH, slowing the three NAD-dependent oxidation steps. Feedback inhibition by succinyl-CoA, citrate, and ATP also slows the cycle by inhibiting early steps. In muscle tissue, Ca2 signals contraction and, as shown here, stimulates energy-yielding metabolism to replace the ATP consumed by contraction.

# Summery of Regulation of the Citric Acid Cycle

- The overall rate of the citric acid cycle is controlled by the rate of conversion of pyruvate to acetyl-CoA and by the flux through citrate synthase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase. These fluxes are largely determined by the concentrations of substrates and products: the end products ATP and NADH are inhibitory, and the substrates NAD and ADP are stimulatory.

- The production of acetyl-CoA for the citric acid cycle by the PDH complex is inhibited allosterically by metabolites that signal a sufficiency of metabolic energy (ATP, acetyl-CoA, NADH, and fatty acids) and stimulated by metabolites that indicate a reduced energy supply (AMP, NAD, CoA).

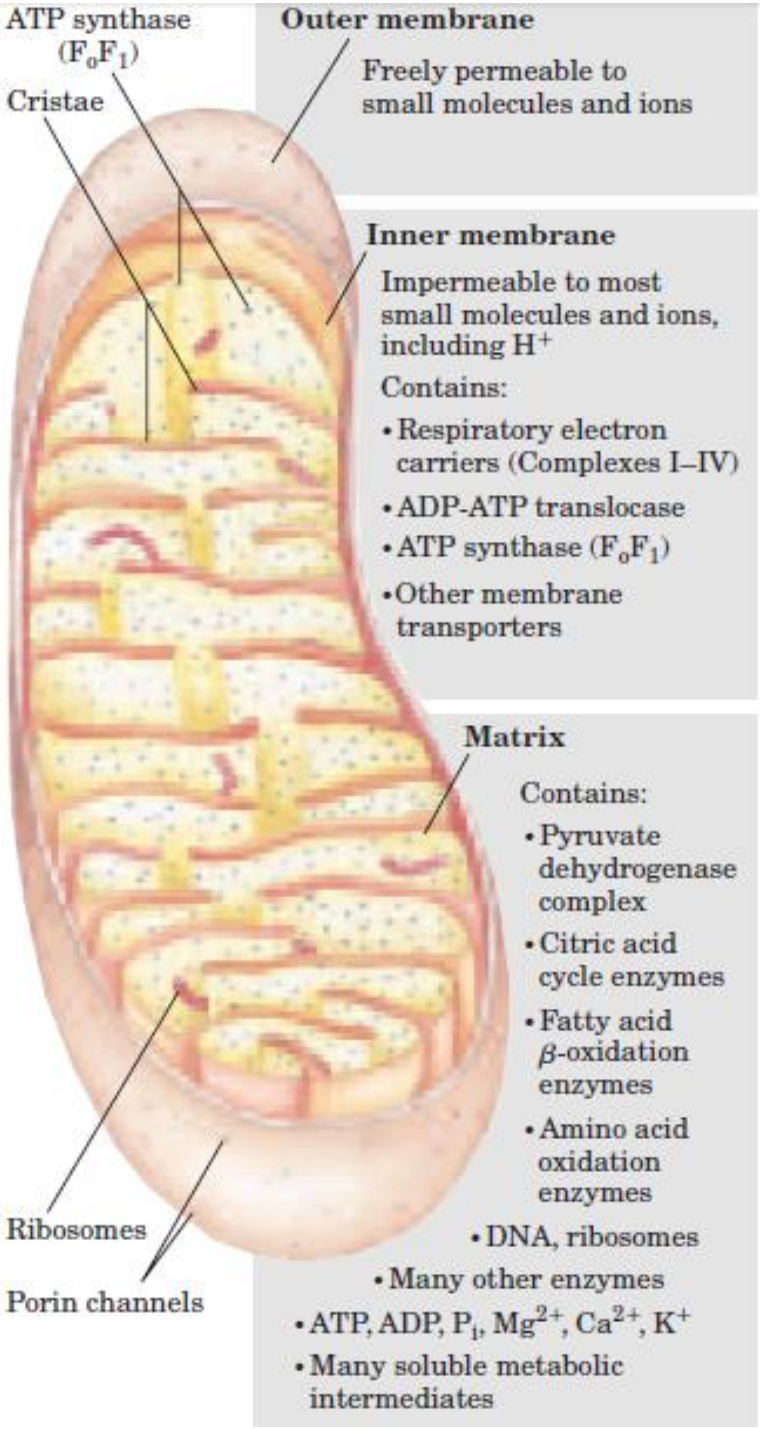
# Significance of TCA cycle

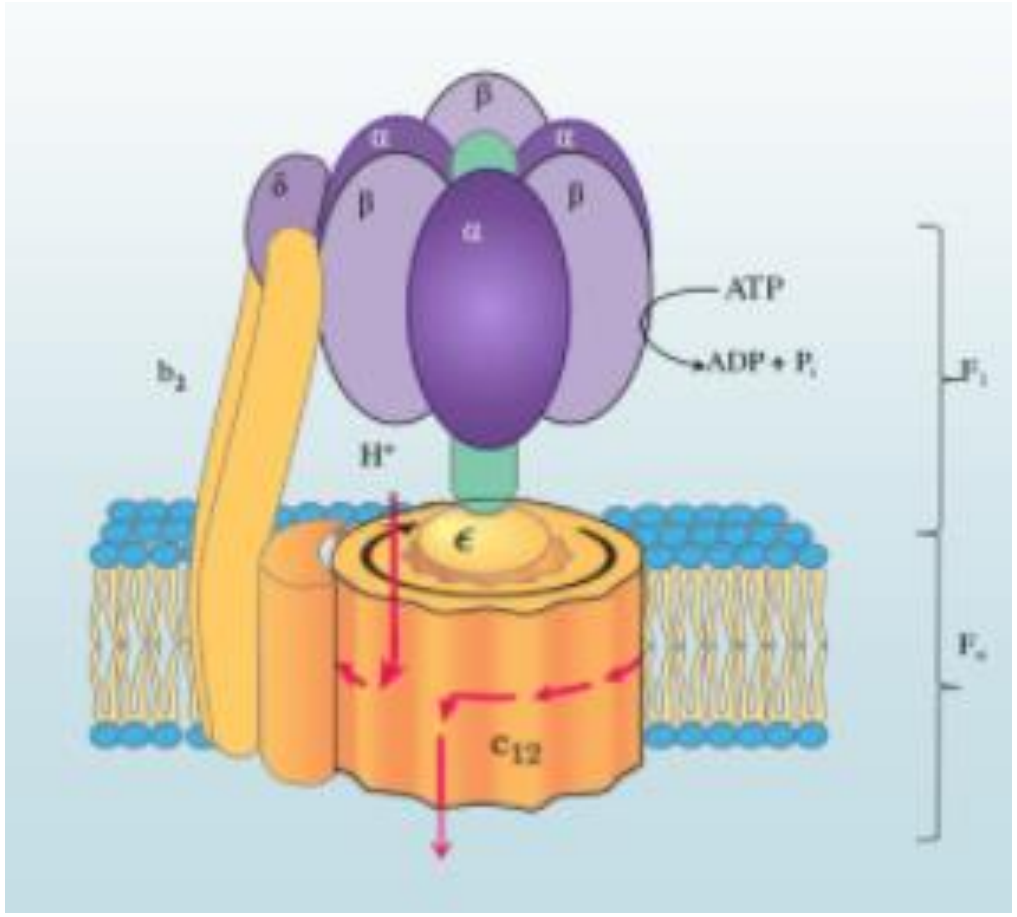
- Complete oxidation of acetyl CoA.
- ATP generation.
- Final common oxidative pathway.
- Integration of major metabolic pathways.
- Fat is burned on the wick of carbohydrates.
- Excess carbohydrates are converted as neutral fat
- No net synthesis of carbohydrates from fat.
- Carbon skeleton of amino acids finally enter the TCA cycle.

# Lecture 5 Metabolism
## Electron Transfer Chain & PPP

Dr. Bilal J M Aldahham

# Oxidative phosphorylation



# paradox

aerobic organisms use oxygen to generate the vast amounts of energy required to maintain their metabolic processes, as they risk damage caused by this highly reactive molecule

# Definitions

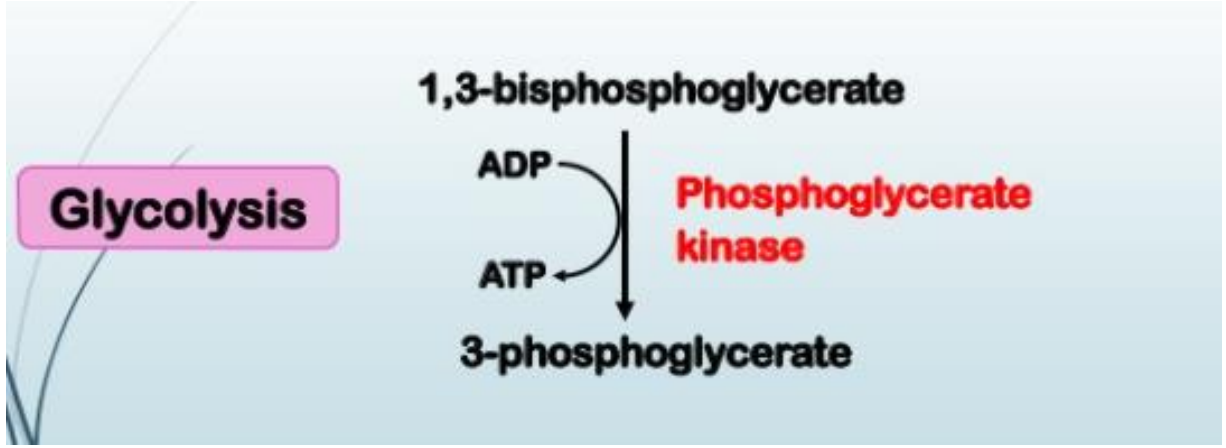
oxidative phosphorylation is the culmination of energy yielding metabolism in aerobic organisms. All oxidative steps in the degradation of carbohydrates, fats, and amino acids converge at this final stage of cellular respiration, in which the energy of oxidation drives the synthesis of ATP. In eukaryotes, oxidative phosphorylation occurs in mitochondria

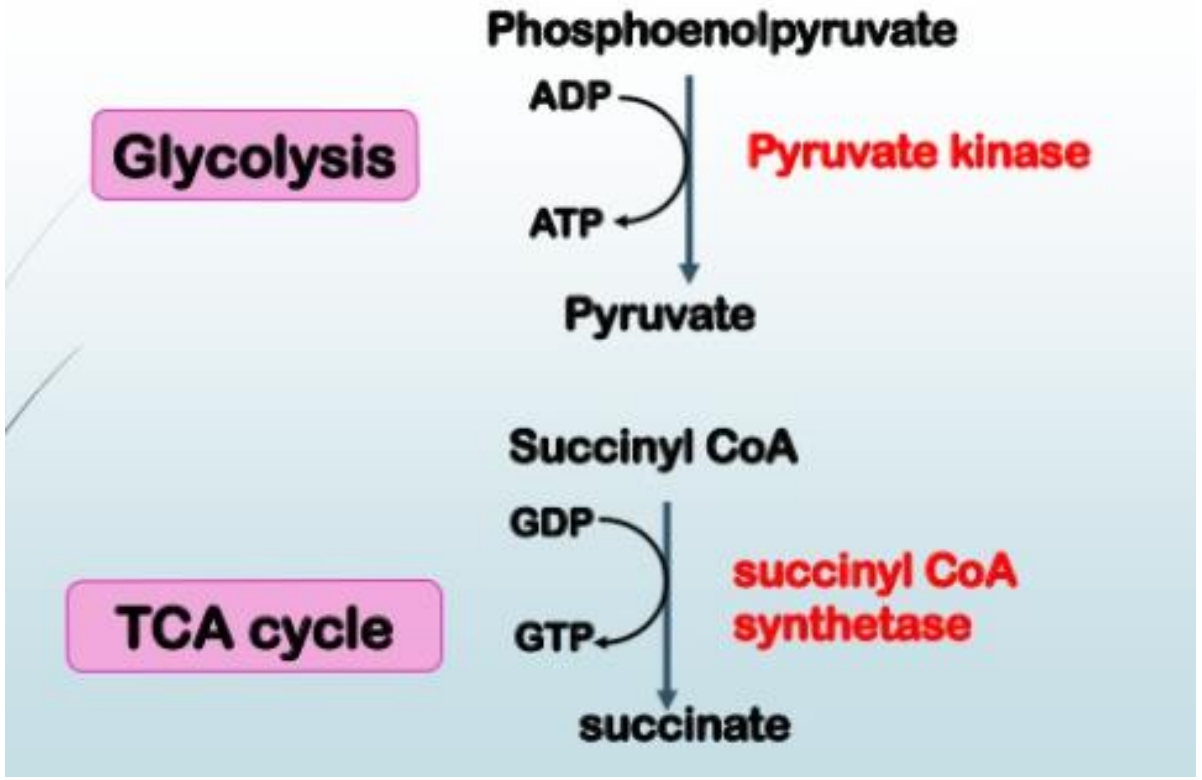
# Types of ATP synthesis

- **Oxidative phosphorylation :**
the phosphorylation of ADP to ATP coupled to electron transfer

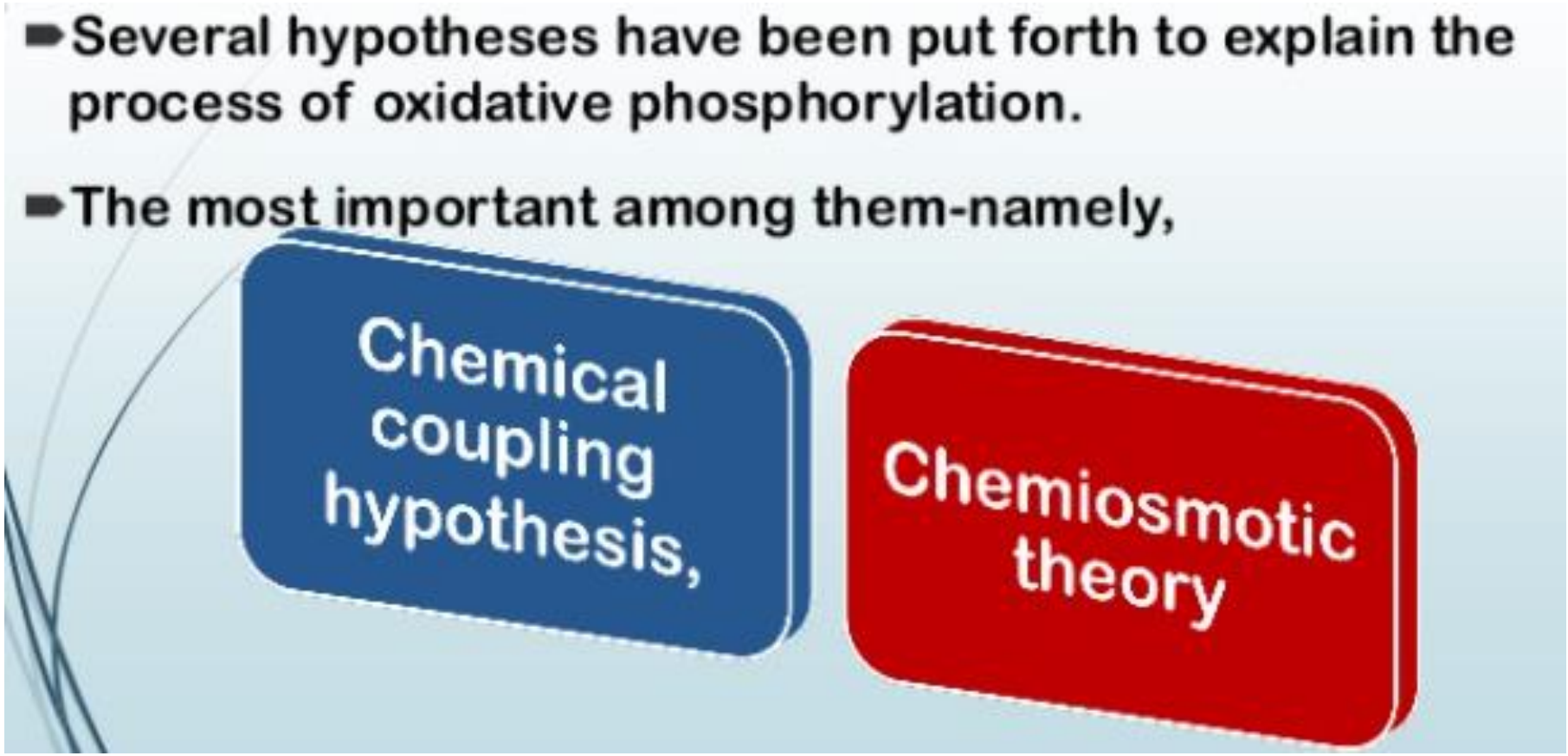
- **Substrate level phosphorylation :**
direct transfer the phosphate from chemical intermediate (also called substrate ) to ADP or GDP forming ATP or GTP, independent of electron transfer chain.

# Examples of substrate level phosphorylation



# Mechanism of oxidative phosphorylation



# Chemiosmotic hypothesis

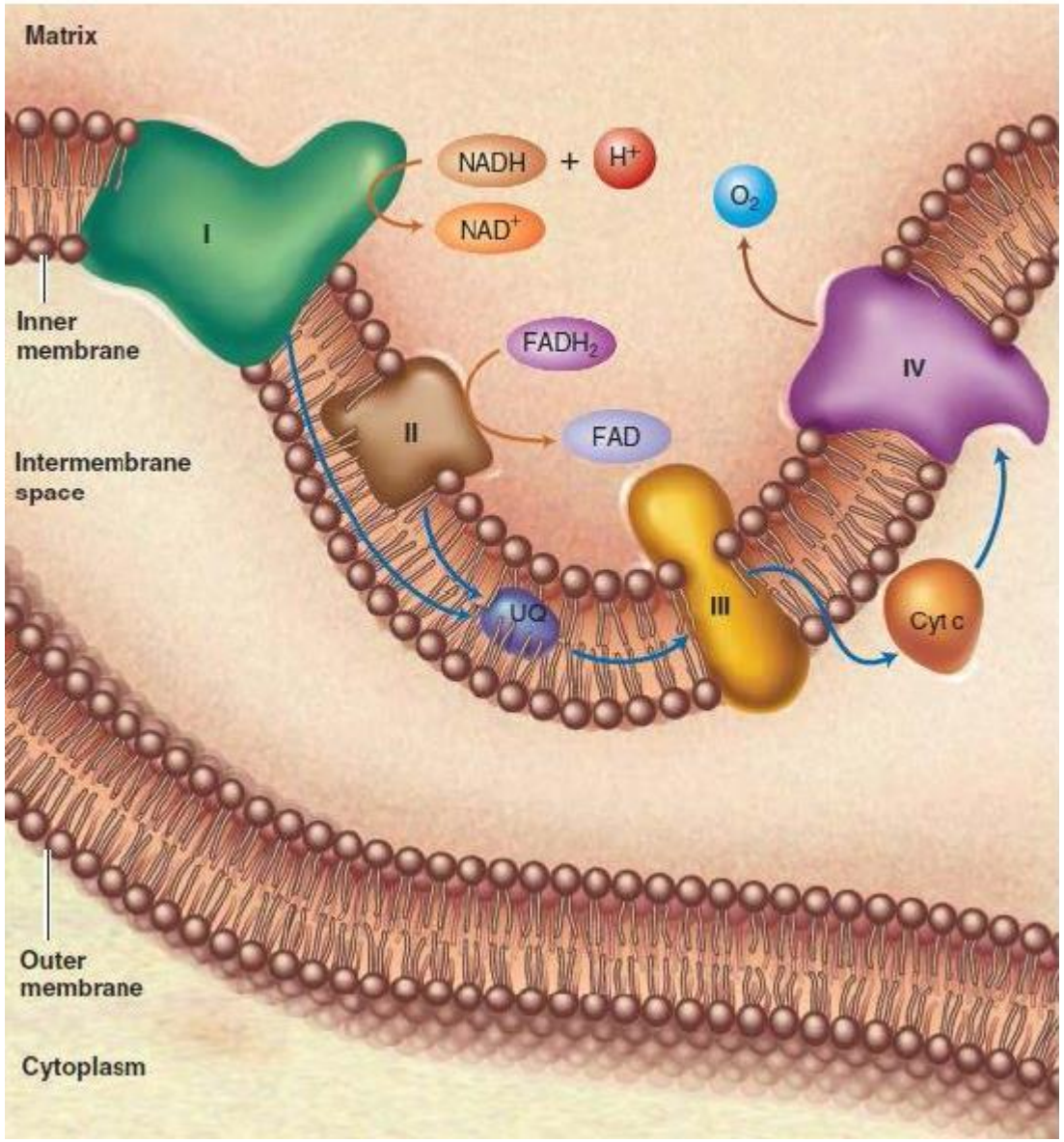
- This hypothesis is the most accepted theory.
- proposed by **Peter Mitchell in 1961**.
- To explain the **oxidative phosphorylation.**
- Nobel Prize, in 1978
- It explains how the transport of electrons through the respiratory chain (ETC) is effectively utilized to produce ATP from ADP + Pi.

Peter Mitchell
**1920-1992**

# Chemiosmotic hypothesis

the energy of electron flow is
conserved by the concomitant pumping of protons across the membrane, producing an electrochemical gradient, the proton-motive force.

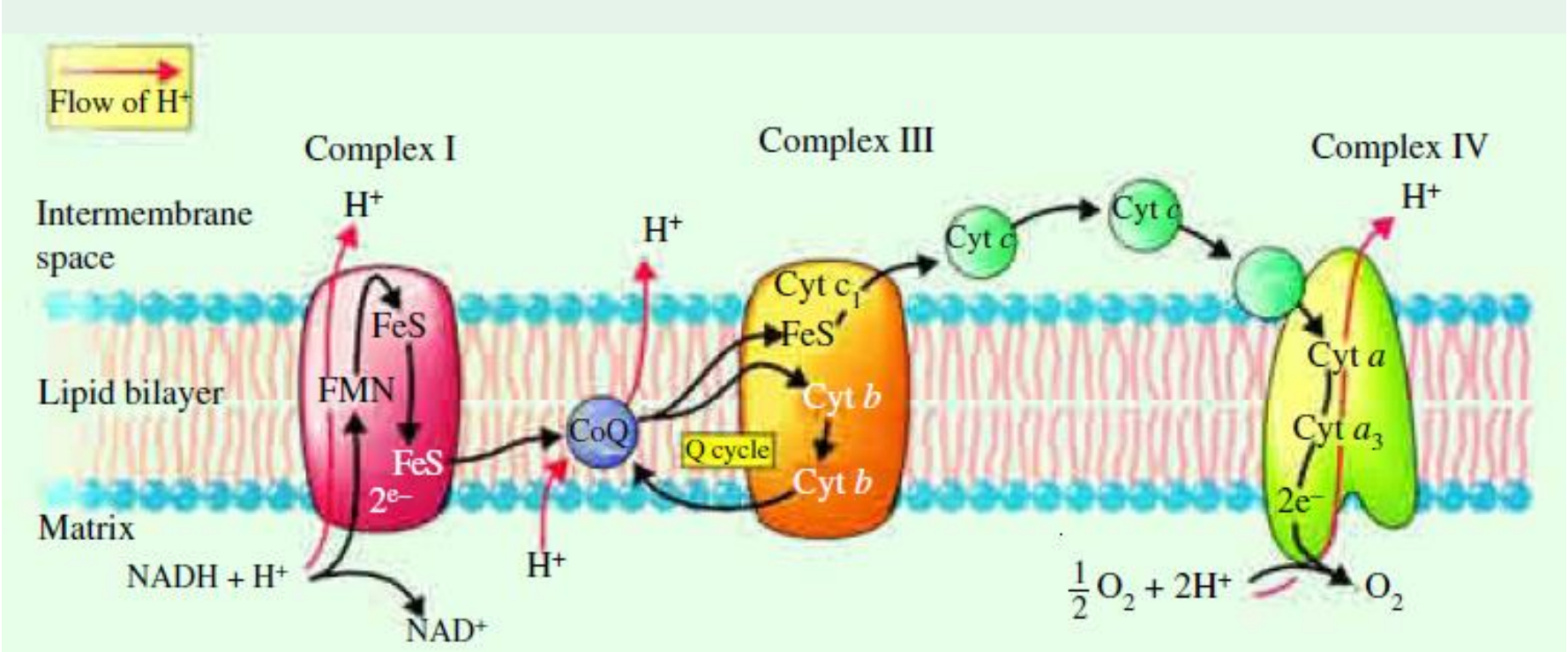
# ETC



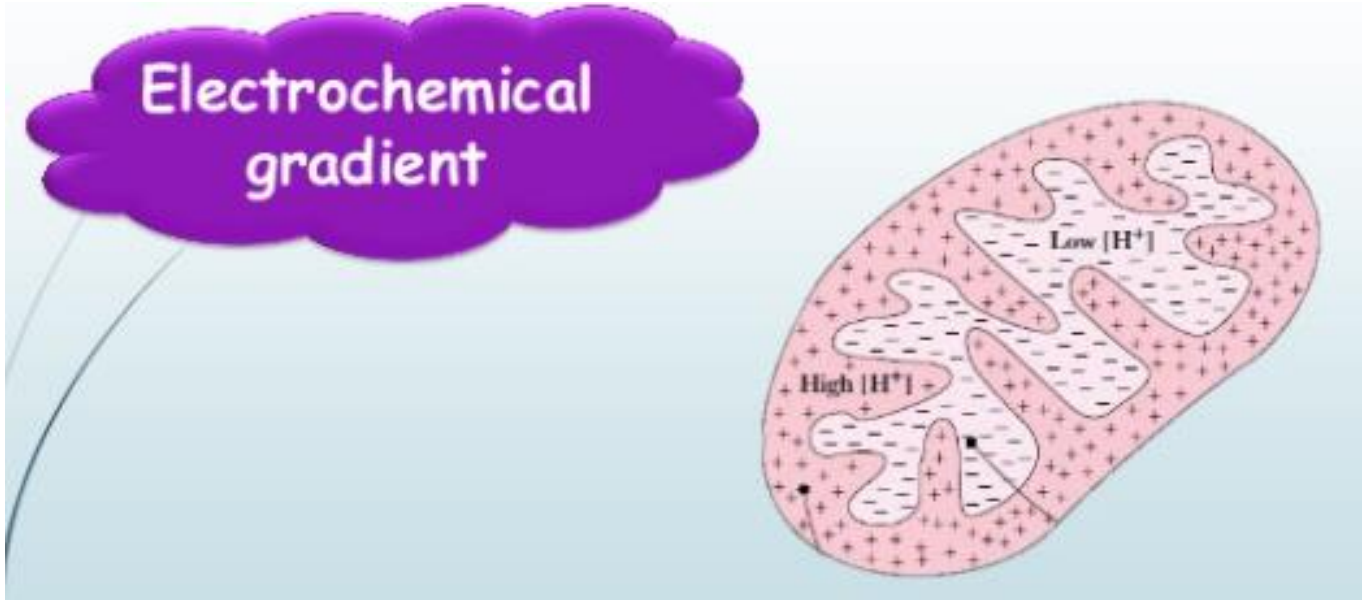

In mitochondria, hydride ions removed from substrates by NAD-linked dehydrogenases donate electrons to the respiratory (electron-transfer) chain, which transfers the electrons to molecular O2, reducing it to H2O

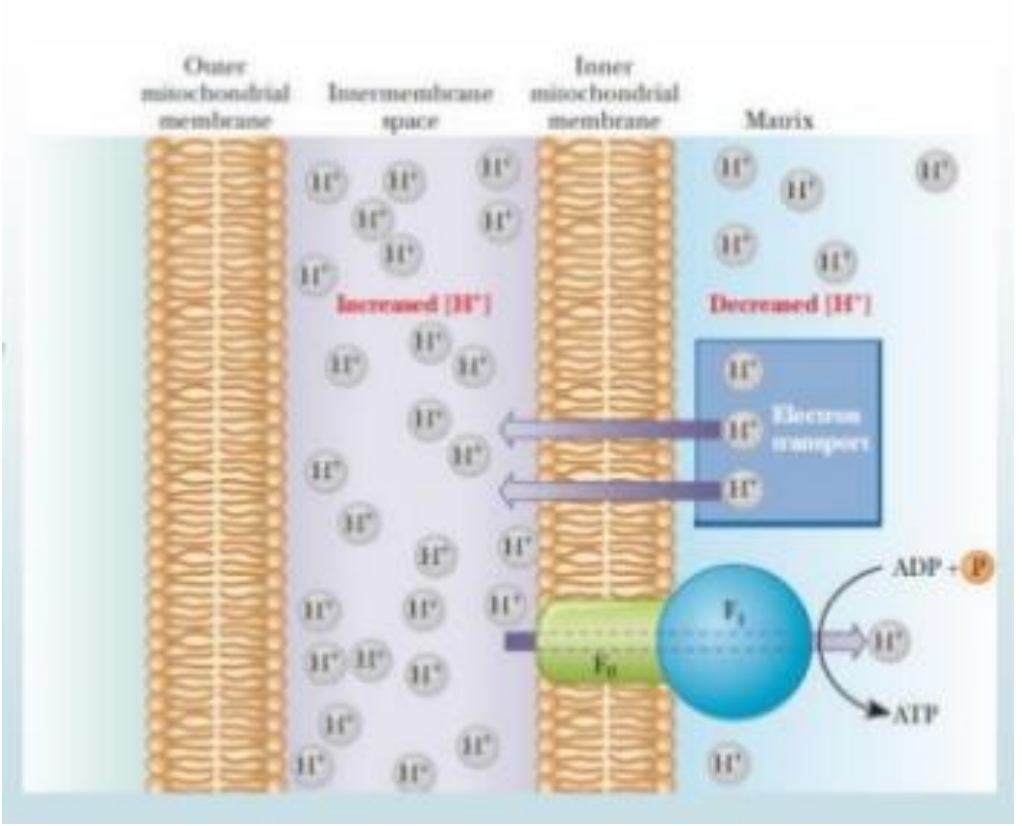
# chemiosmosis

the transfer of electrons through the respiratory chain results in the pumping of protons (H+) from the matrix side (M side) to the cytosol or cytoplasmic side (C-side) of inner mitochondrial membrane The concentration of H+ becomes higher on the cytoplasmic side, thus creating an electrochemical potential difference. This consists of a chemical potential (difference in pH) and a membrane potential, which becomes positive on the cytoplasmic side. The hypothesis further proposes that the H+ ions, ejected by electron transport, flow back into the matrix through a specific H+ channel or 'pore' in the FoF1 ATPase molecule, driven by the concentration gradient of H+. The free energy released, as proton (H+) flows back through the ATPase, causes the coupled synthesis of ATP from ADP and phosphate by ATP synthetase



# Proton motive force

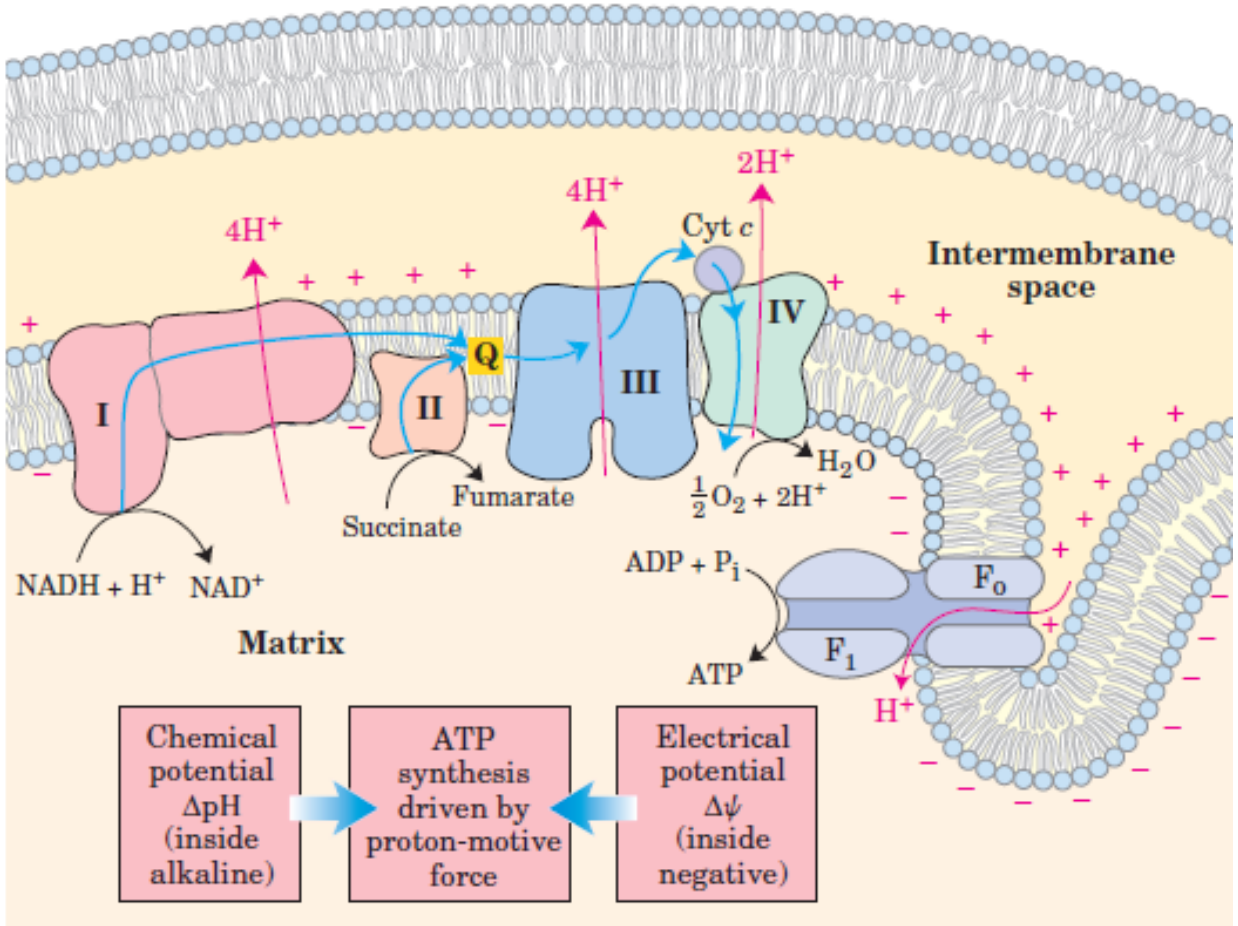


The transfer of two electrons from NADH+ $H^+$ to $O_2$ is accompanied by the outward pumping of 10 $H^+$

Complex I and complex III pumps 4 protons each
Complex IV pumps 2 protons
To inter-membranous space

**10 protons are pumped by the electron transport chain**



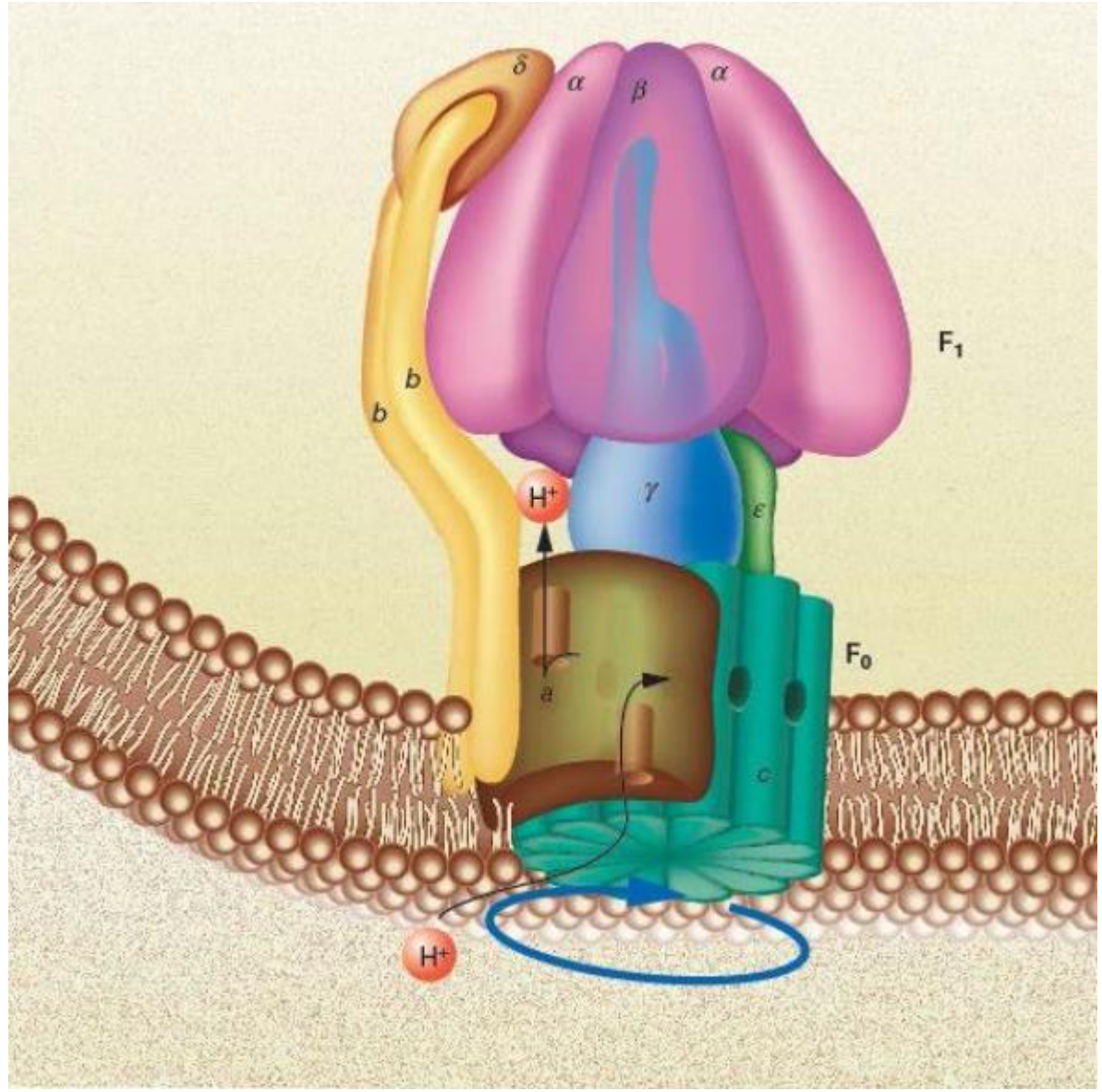

**10 protons are pumped out per NADH**

1. 4 must flow in to produce 1 ATP
2. The proton-based P/O ratio is 2.5 for NADH as the electron donor and 1.5 (6/4) for succinate

# ATP generation

**TABLE 20.4:** ATP generation, old and new values

| *ATP generation by oxidation of* | *Old value* | *Presently accepted* |
|---|---|---|
| NADH | 3 | 2.5 |
| FADH | 2 | 1.5 |
| Glucose | 38 | 32 |
| Acetyl CoA | 12 | 10 |
| Palmitate | 129 | 106 |


δ
α
β
α
F1
b
b
b
H+
γ
ε
F0
a
c
H+

# summery

The flow of electrons through Complexes I, III, and IV results in pumping of protons across the inner mitochondrial membrane, making the matrix alkaline relative to the intermembrane space. This proton gradient provides the energy (in the form of the proton-motive force) for ATP synthesis from ADP and Pi by ATP synthase (FoF1 complex) in the inner membrane.

ATP formation on the enzyme requires little
energy; the role of the proton-motive force is to push ATP from its binding site on the synthase.

ATP synthase carries out "rotational catalysis," in which the flow of protons through Fo causes each of three nucleotide-binding sites in F1 to cycle from (ADP  Pi)–bound to ATP-bound to empty conformations.

The ratio of ATP synthesized per  1 $2O_2$ reduced to $H_2O$ (the P/O ratio) is about 2.5 when electrons enter the respiratory chain at Complex I, and 1.5 when electrons enter at CoQ

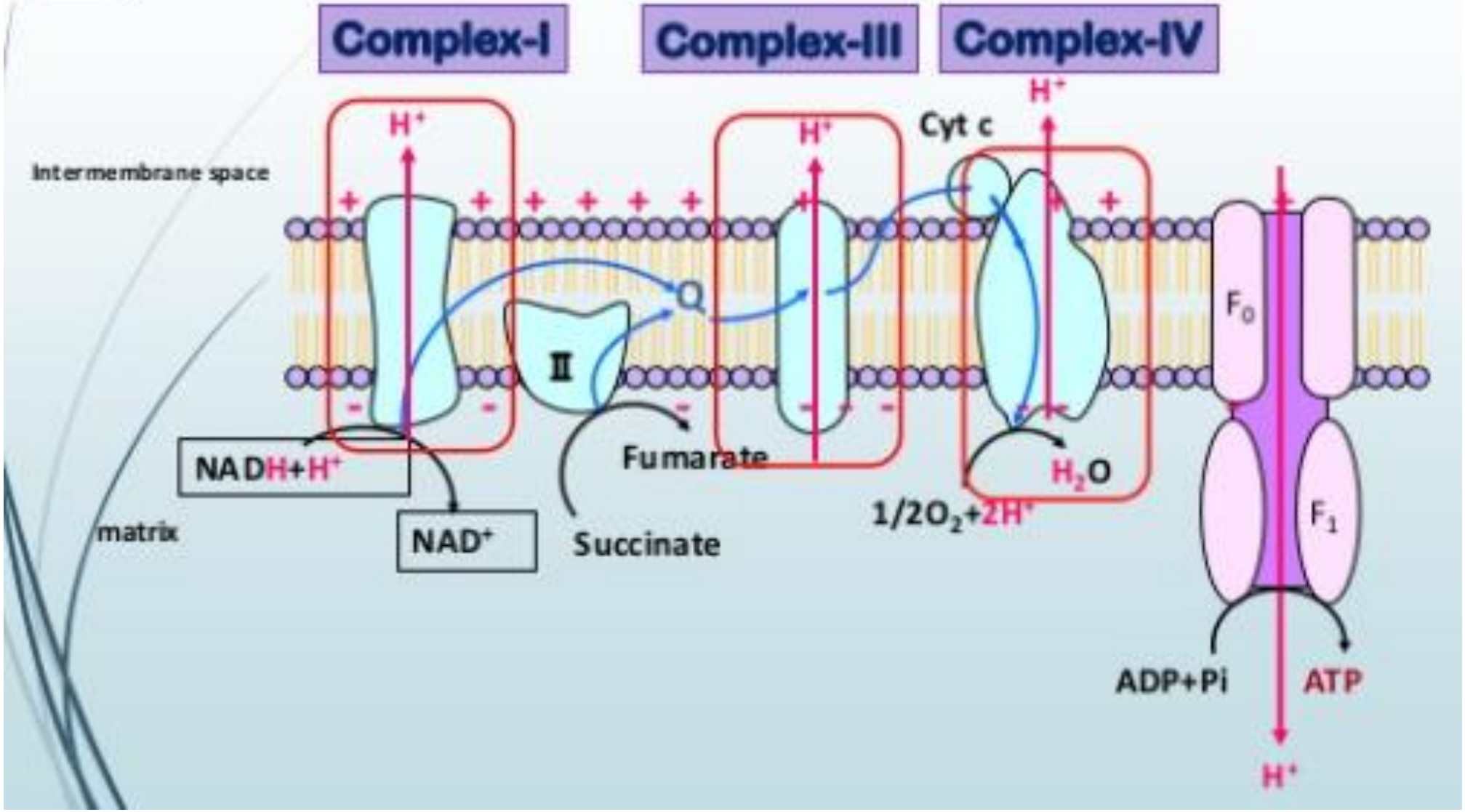
# P:O ratio

- The **P:O ratio** refers to the number of **inorganic phosphate** molecules incorporated into ATP for every atom of oxygen consumed.
- When a pair of electrons from NADH reduces an atom of oxygen (½ $O_2$), 2.5 mol of ATP are formed per 0.5 mol of $O_2$ consumed.
- This results in conversion of energy required for production of only ***3*** ATP from NADH and 2 ATP from $FADH_2$

- The mitochondrial oxidation of NADH with a classical **P : O ratio of 3** can be represented by the following equation :

$$NADH + H^+ + \tfrac{1}{2} O_2 + 3ADP + 3Pi \rightarrow NAD^+ + 3ATP + H_2O$$

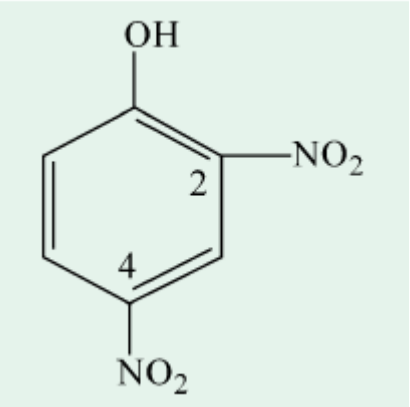
# Coupling sites for ATP synthesis.



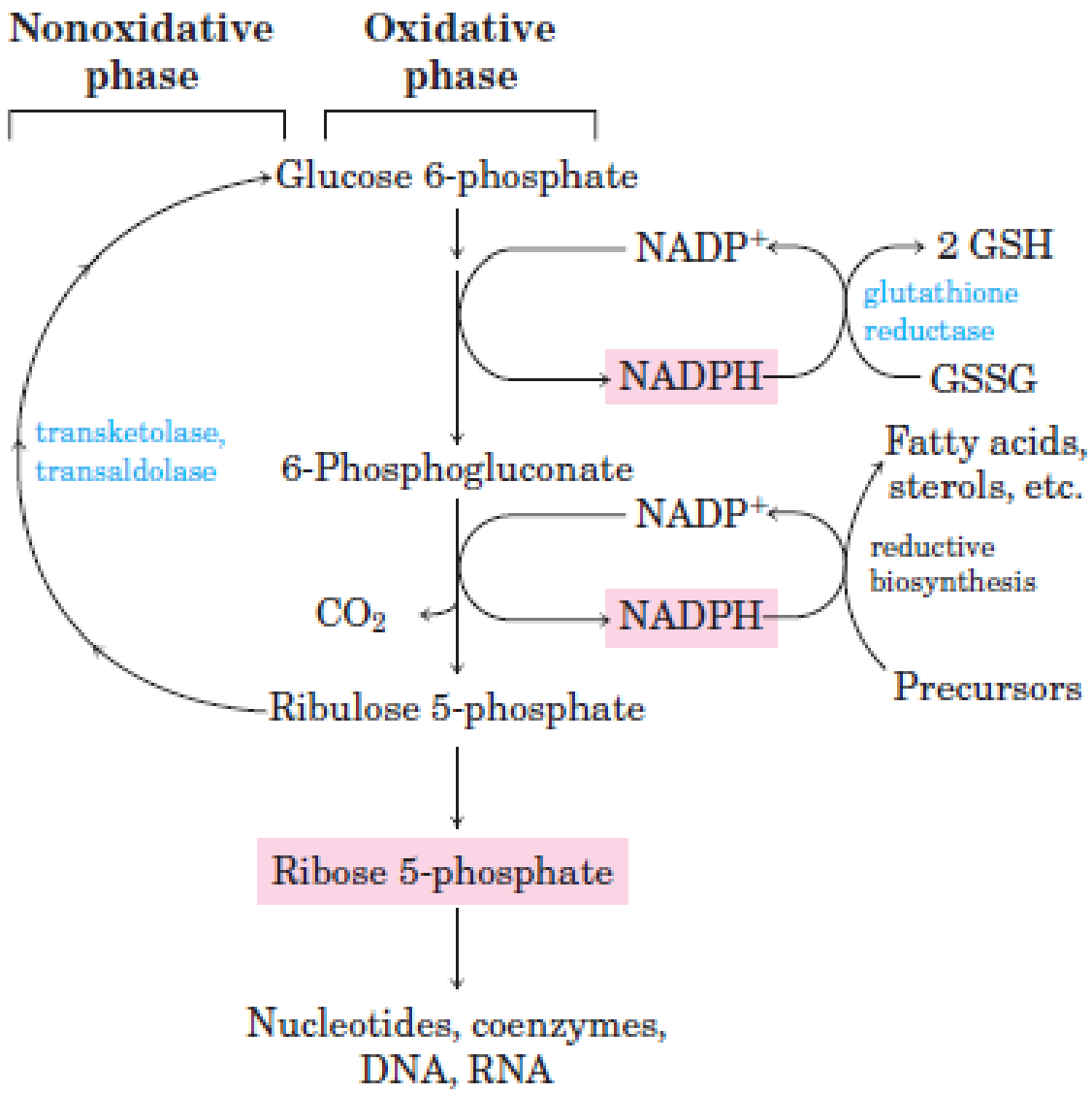
# Regulation of Oxidative Phosphorylation

Oxidative phosphorylation is regulated by cellular energy demands. The intracellular [ADP] and the mass-action ratio [ATP]/([ADP][Pi]) are measures of a cell's energy status.

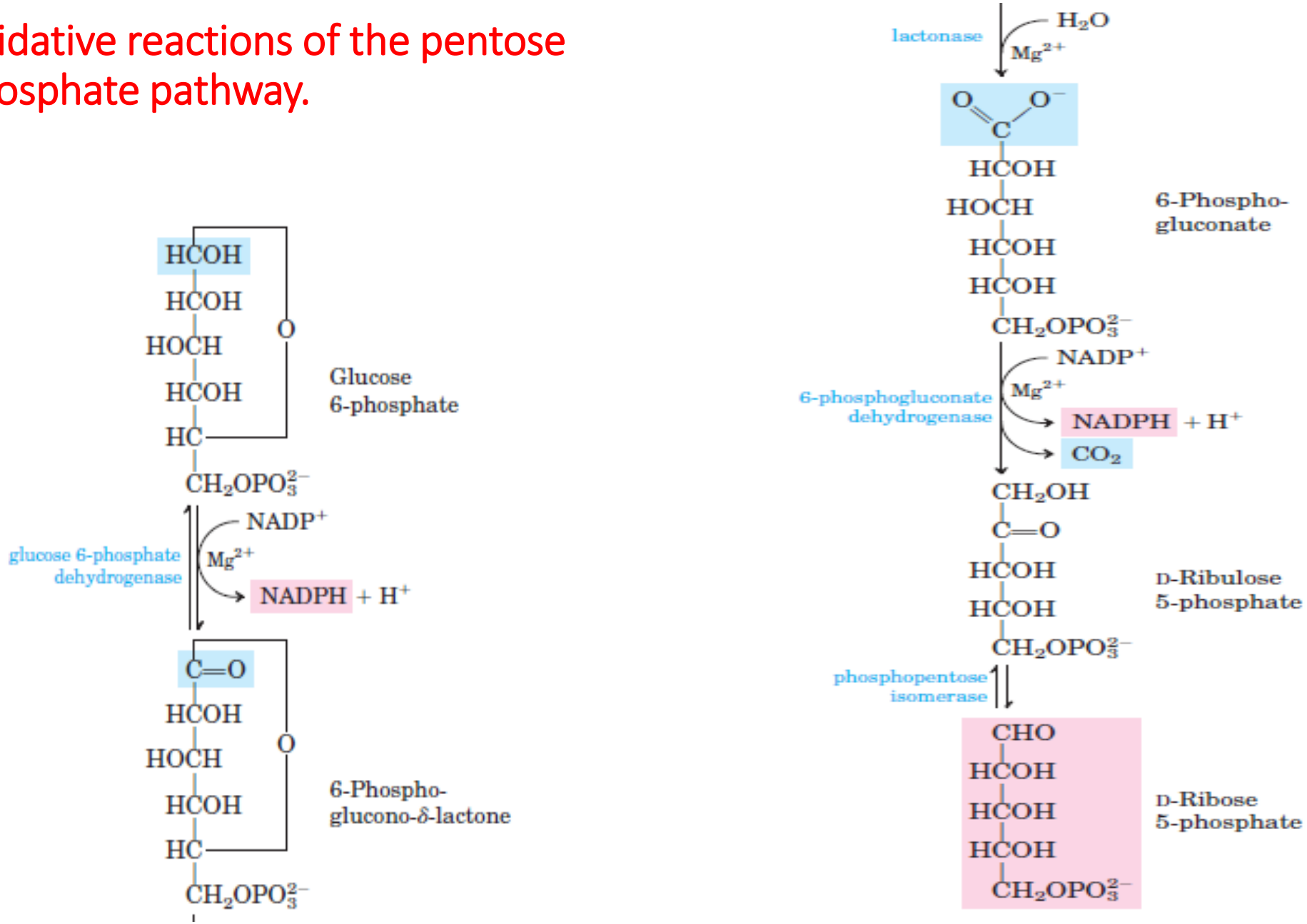
- Uncoupling agents are compounds which dissociate (or 'uncouple') the synthesis of ATP from the transport of electrons through the cytochrome system



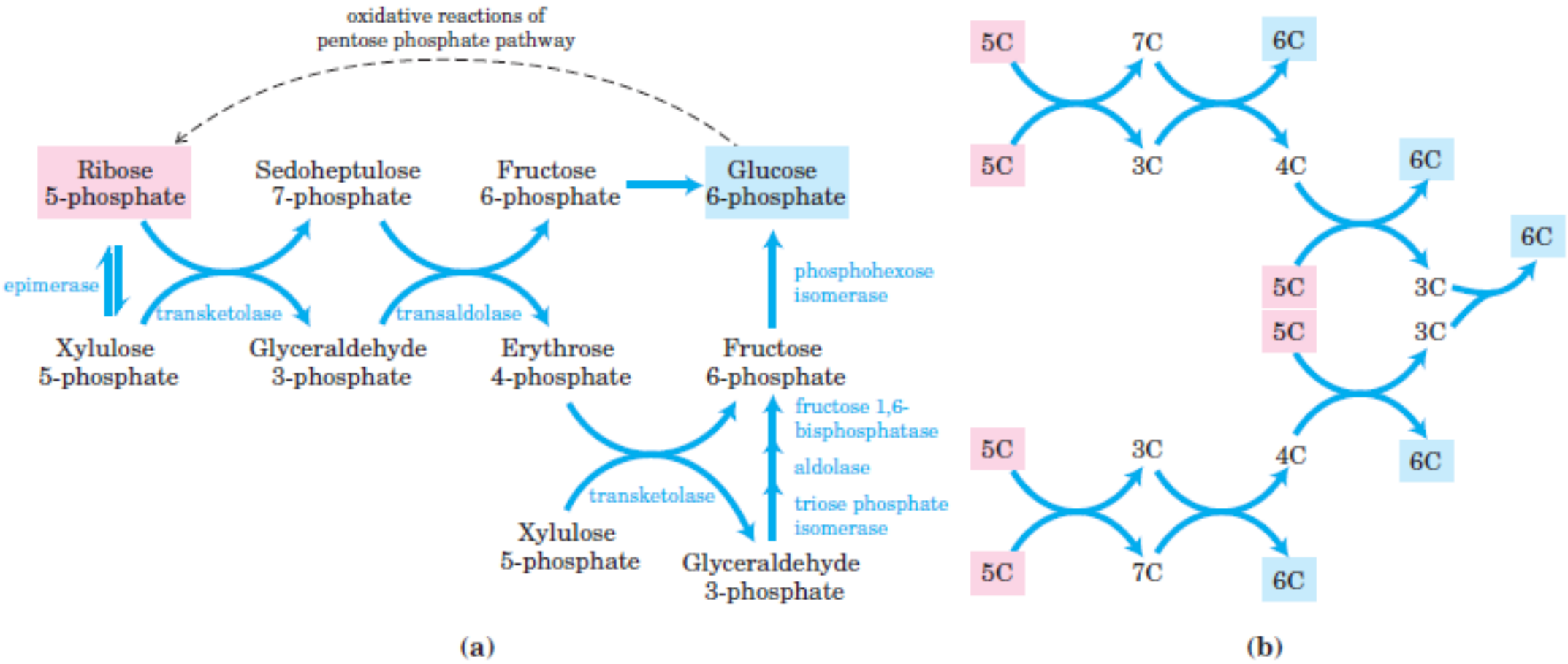
# General scheme of the pentose phosphate pathway



# Oxidative reactions of the pentose phosphate pathway.



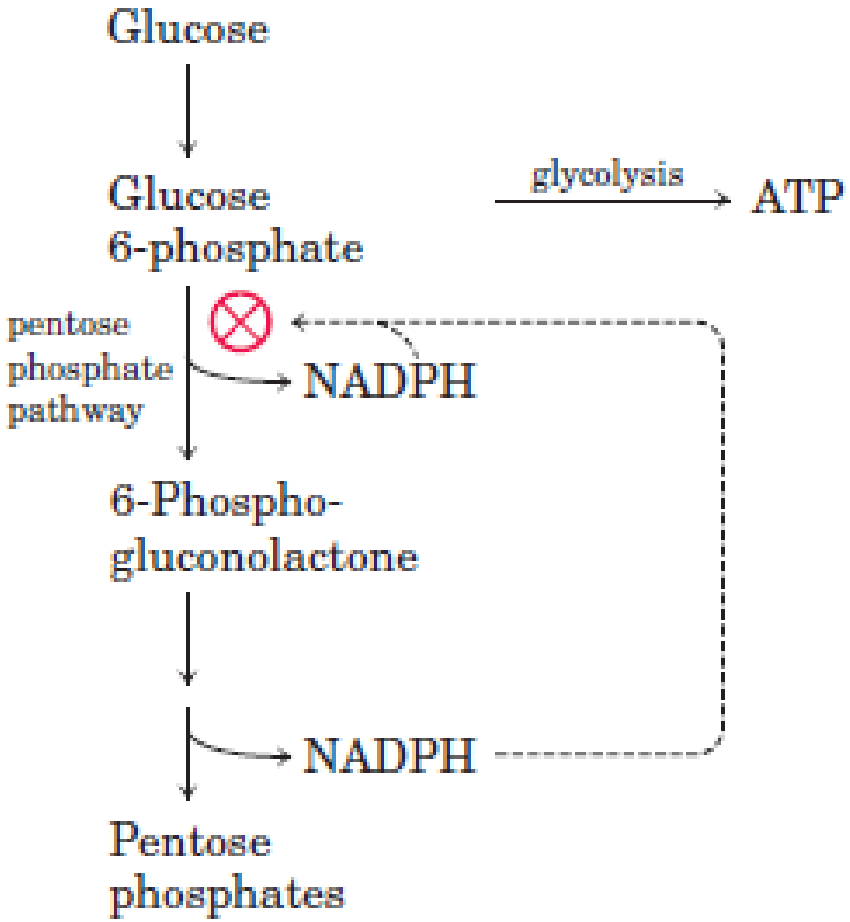
# Nonoxidative reactions of the pentose phosphate pathway



# Role of NADPH in regulating the partitioning of glucose 6-phosphate between glycolysis and the pentose phosphate pathway

When NADPH is forming faster than it is being used for biosynthesis and glutathione reduction (see Fig. 14–20), [NADPH] rises and inhibits the first enzyme in the pentose phosphate pathway.

As a result, more glucose 6-phosphate is available for glycolysis.



# summery

- The first phase of the pentose phosphate pathway consists of two oxidations that convert glucose 6-phosphate to ribulose 5-phosphate and reduce $NADP^+$ to NADPH. The second phase comprises nonoxidative steps that convert pentose phosphates to glucose 6-phosphate, which begins the cycle again.
- In the second phase, transaldolase (with TPP as cofactor) and transketolase catalyze the interconversion of three-, four-, five-, six-, and seven-carbon sugars, with the reversible conversion of six pentose phosphates to five hexose phosphates.
- when the body doesn't have enough of an enzyme called G6PD (glucose-6-phosphate dehydrogenase). This enzyme helps red blood cells work properly. A lack of this enzyme can cause hemolytic anemia. This is when the red blood cells break down faster than they are made.

# Lecture 6
# Lipid Metabolism I

## Digestion, Transport, and β-oxidation

Dr. Bilal J M Aldahham

# Overview

- LIPIDS PLAY A UNIQUE ROLE IN LIVING ORGANISMS LARGELY BECAUSE OF THEIR HYDROPHOBIC STRUCTURES
- LIPIDS SERVE AS:

1. HIGHLY EFFICIENT AND compact energy storage molecules (triacylglycerols)

2. essential components of biological membranes (phospholipids, sphingolipids, and cholesterol)

- 3. diverse molecules that have signaling (e.g., steroid hormones and prostaglandins) or protective (e.g., $\alpha$-tocopherol) functions

# Overview

- The oxidation of long-chain fatty acids to acetyl-CoA is a central energy-yielding pathway in many organisms and tissues.

- In mammalian heart and liver, for example, it provides as much as 80% of the energetic needs under all physiological circumstances.

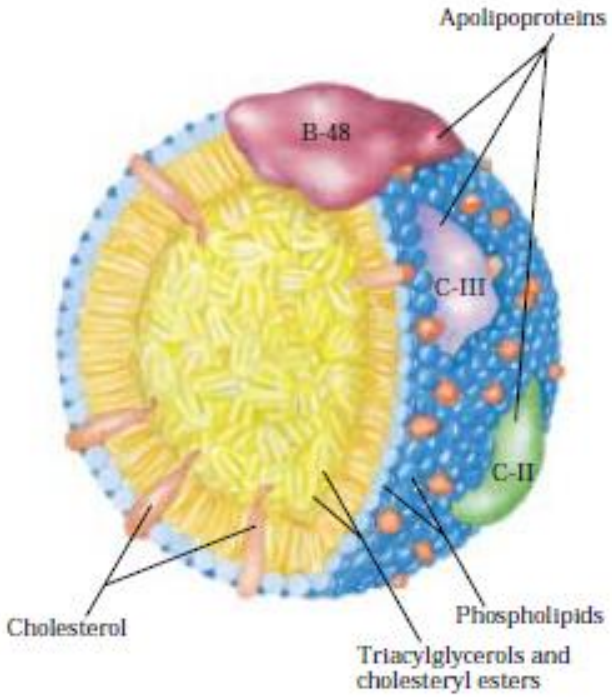
- The electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis; the acetyl-CoA produced from the fatty acids may be completely oxidized to CO2 in the citric acid cycle, resulting in further energy conservation.

# Basics

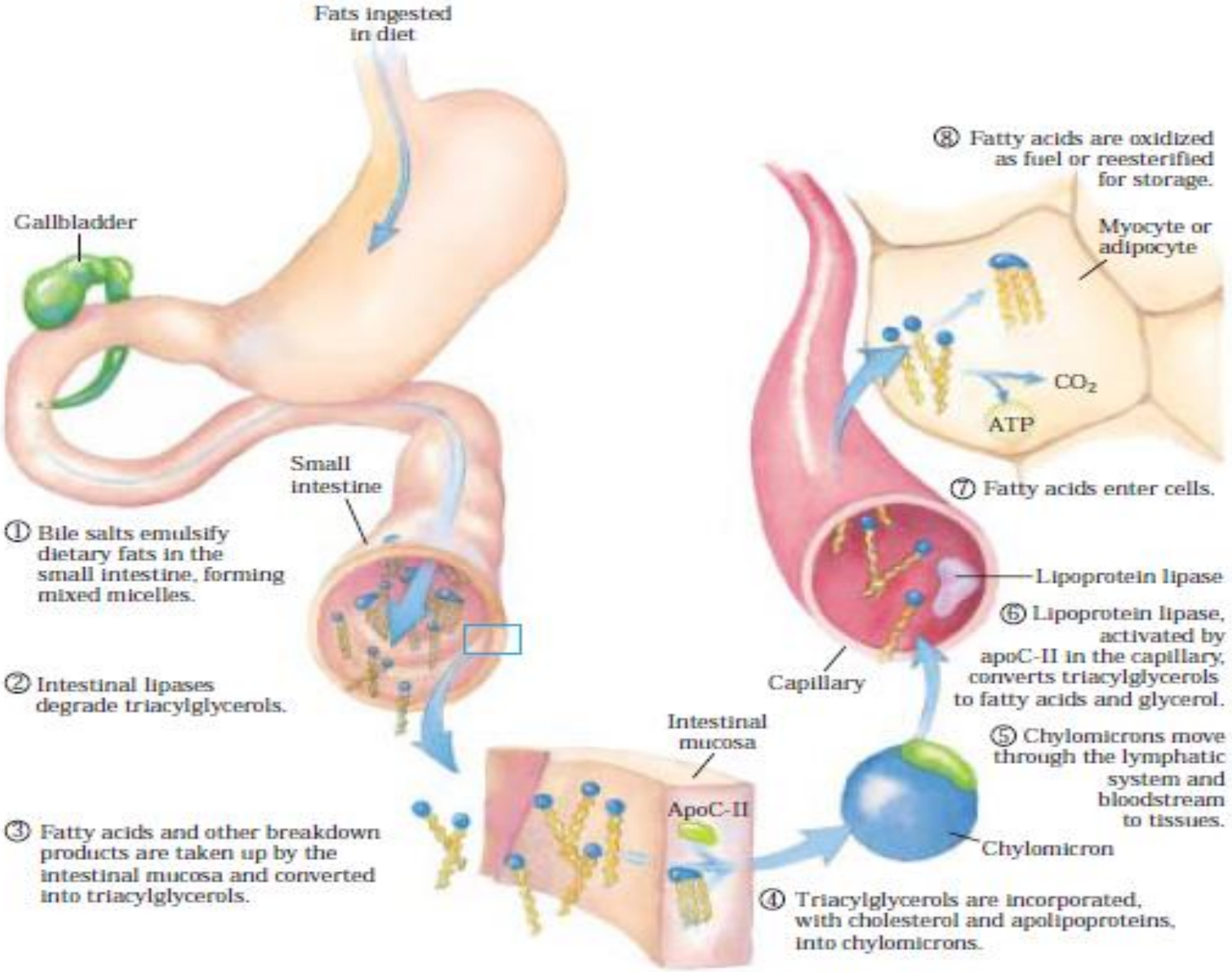
- In liver, acetyl-CoA may be converted to ketone bodies— water-soluble fuels exported to the brain and other tissues when glucose is not available.

- Although the biological role of fatty acid oxidation differs from organism to organism, the mechanism is essentially the same. The repetitive four-step process, called **oxidation,** by which fatty acids are converted into acetyl-CoA
- Chemical steps of fatty acid oxidation in mitochondria. The complete oxidation of fatty acids to CO2 and H2O takes place in three stages: the oxidation of long-chain fatty acids to two-carbon fragments, in the form of acetyl-CoA ( oxidation); the oxidation of acetyl-CoA to CO2 in the citric acid cycle and the transfer of electrons from reduced electron carriers to the mitochondrial respiratory chain

# Processing of dietary lipids in vertebrates

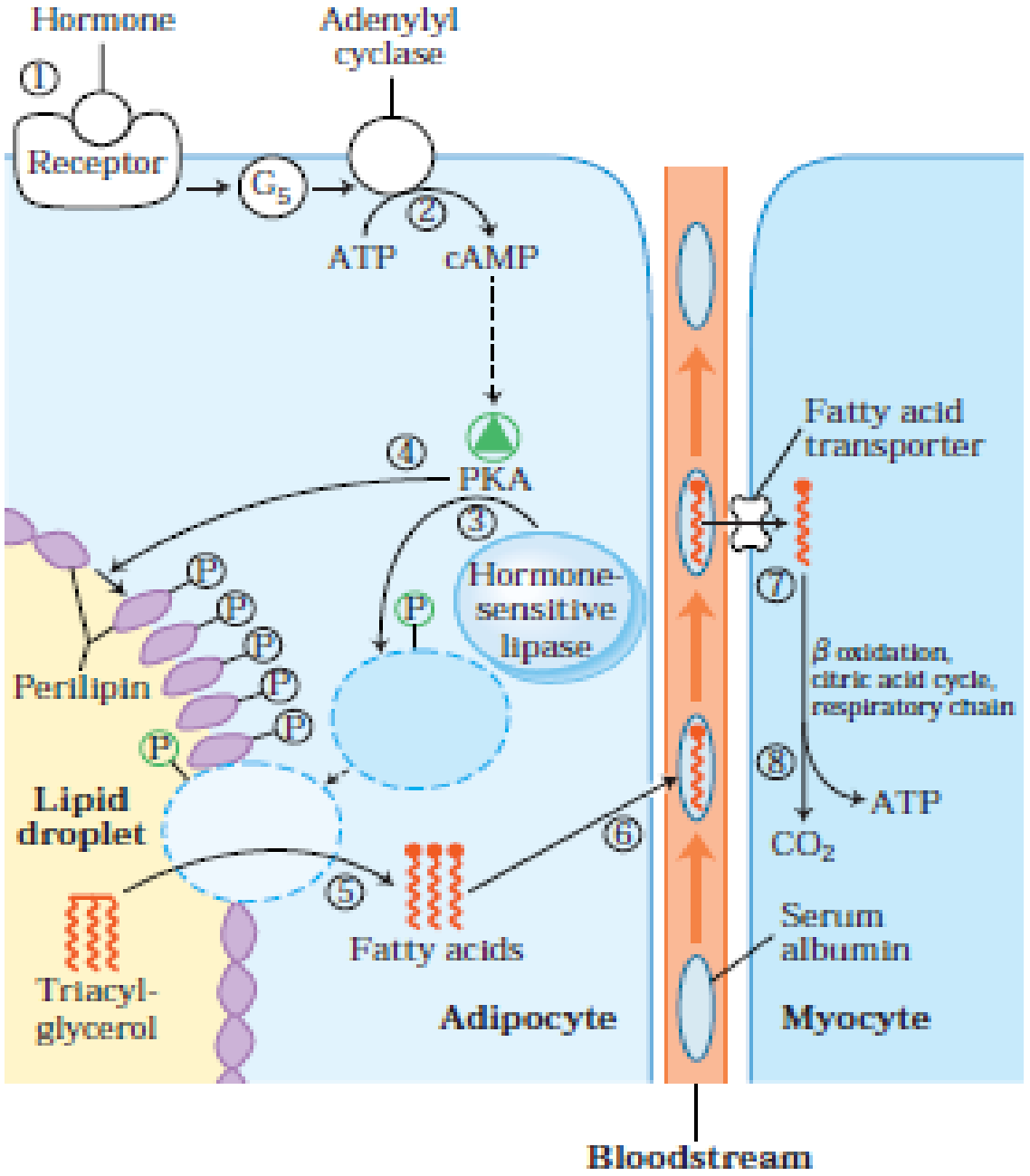



Chylomicron

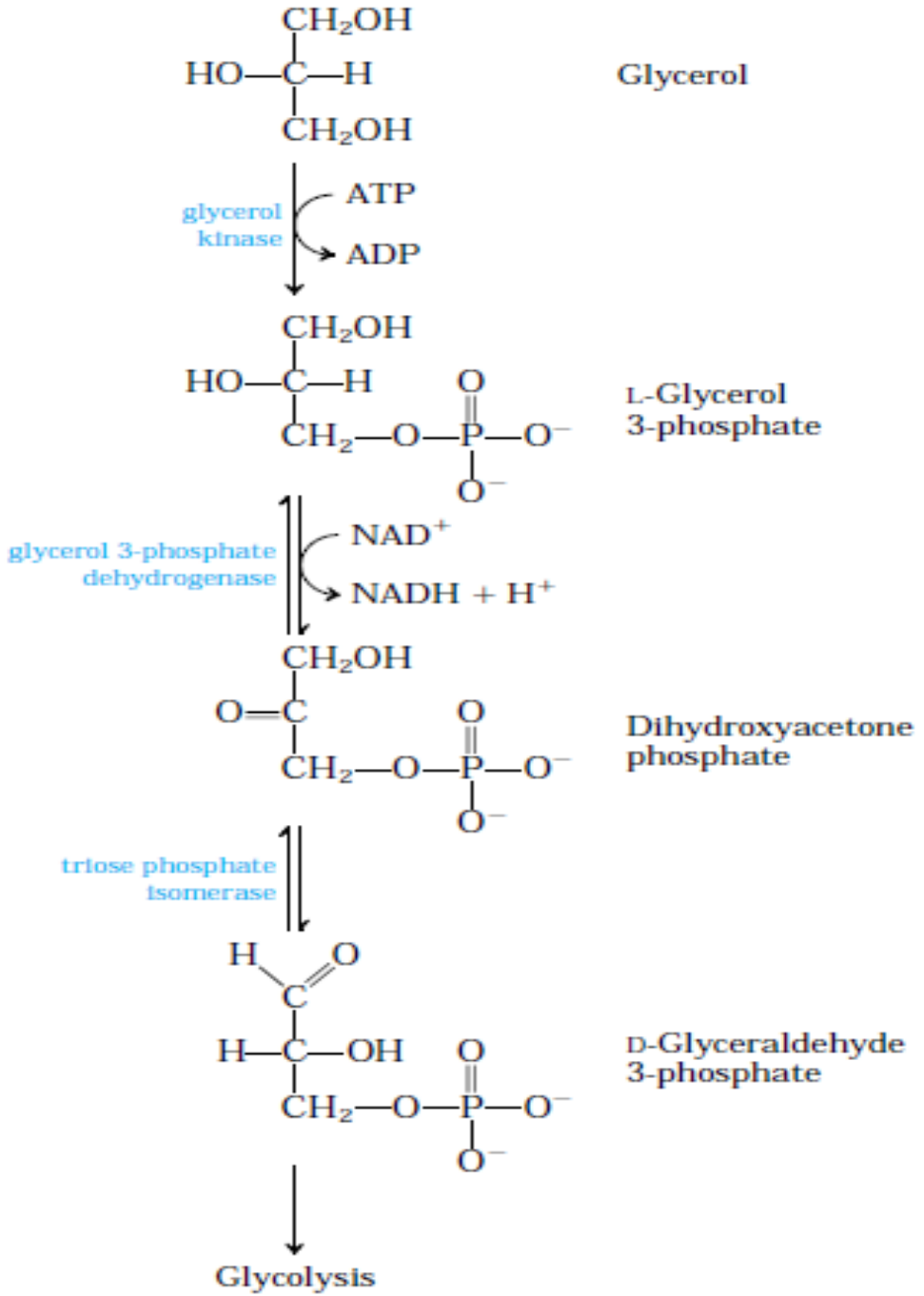


# Mobilization of triacylglycerols stored in adipose tissue

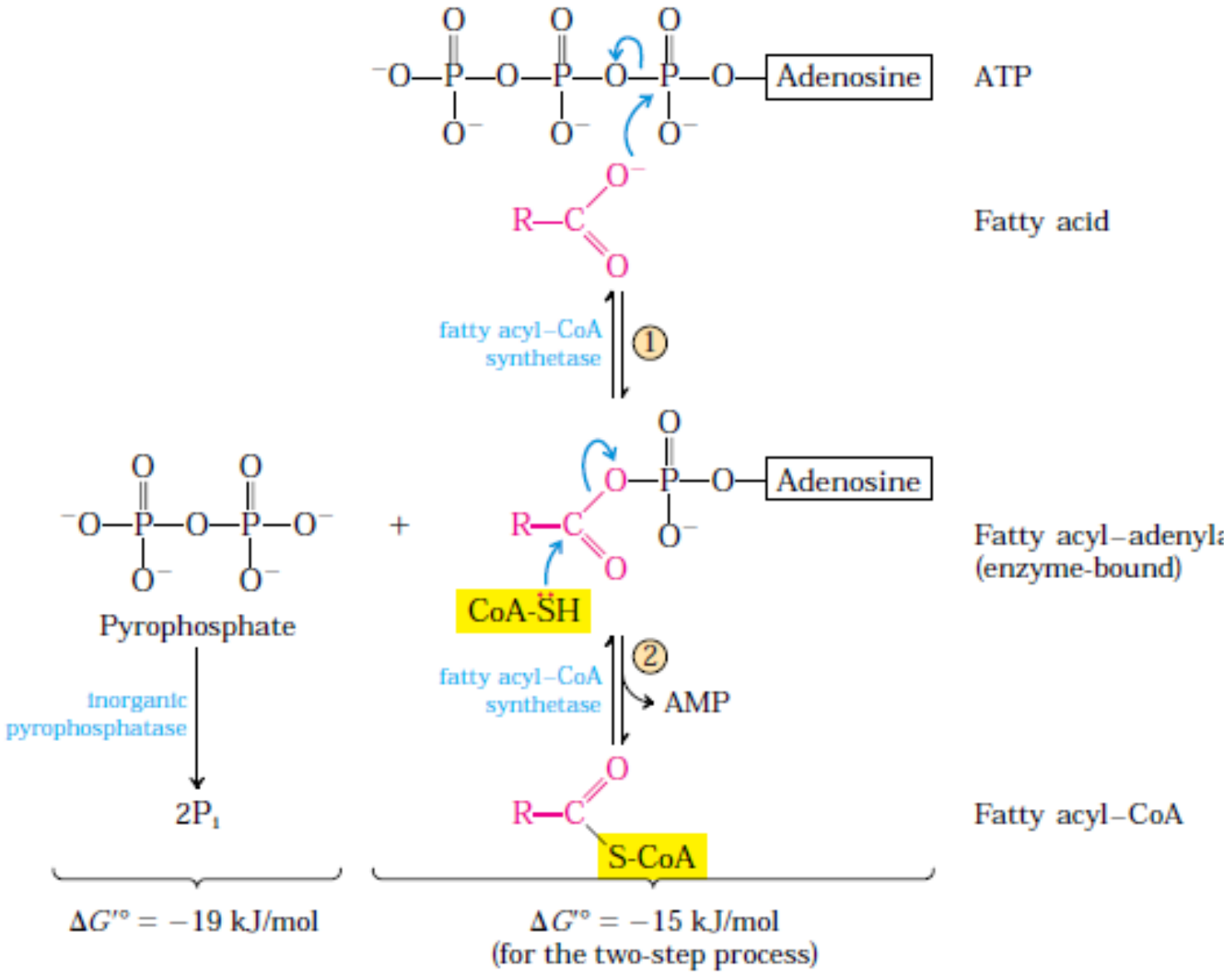
When low levels of glucose in the blood trigger the release of glucagon, 1 the hormone binds its receptor in the adipocyte membrane and thus 2 stimulates adenylyl cyclase, via a G protein, to produce cAMP. This activates PKA, which phosphorylates 3 the hormone-sensitive lipase and 4 perilipin molecules on the surface of the lipid droplet. Phosphorylation of perilipin permits hormone sensitive lipase access to the surface of the lipid droplet, where 5 it hydrolyzes triacylglycerols to free fatty acids. 6 Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood; they are released from the albumin and 7 enter a myocyte via a specific fatty acid transporter. 8 In the myocyte, fatty acids are oxidized to $CO_2$, and the energy of oxidation is conserved in ATP, which fuels muscle contraction and other energy requiring metabolism in the myocyte



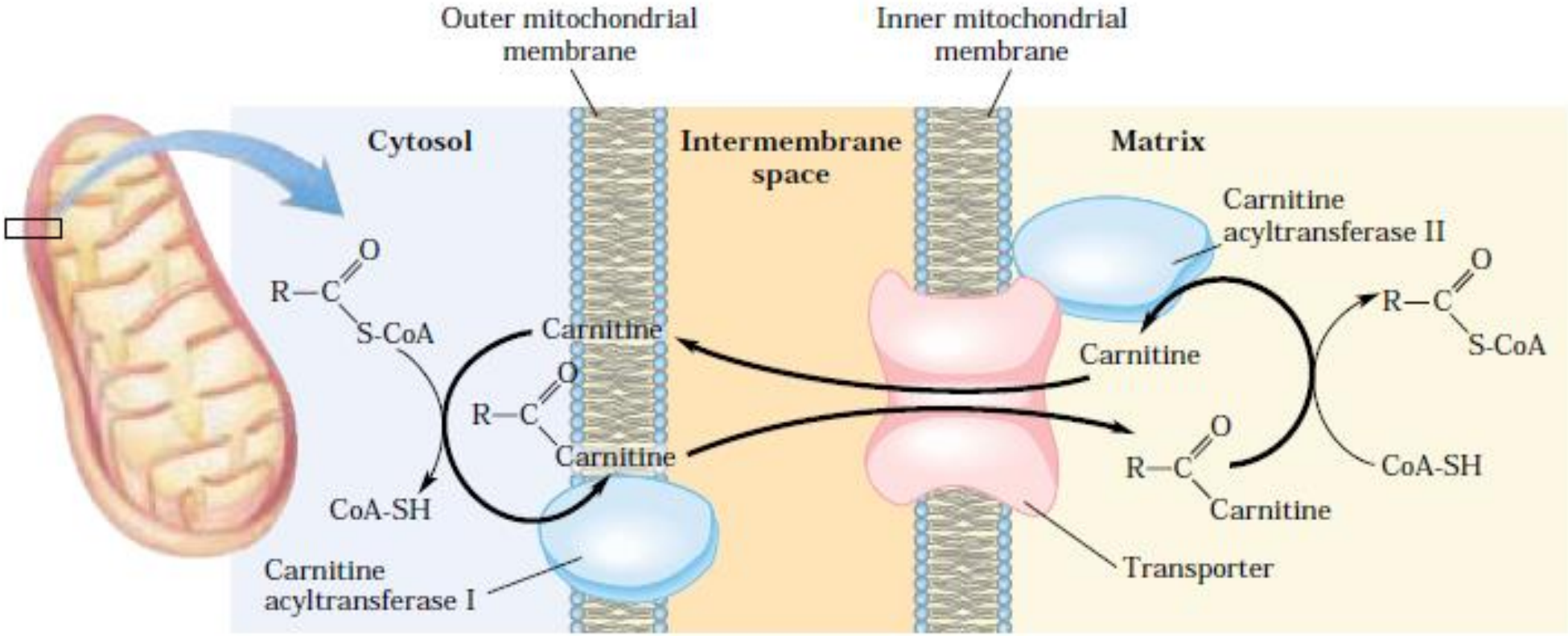
# Entry of glycerol into the glycolytic pathway

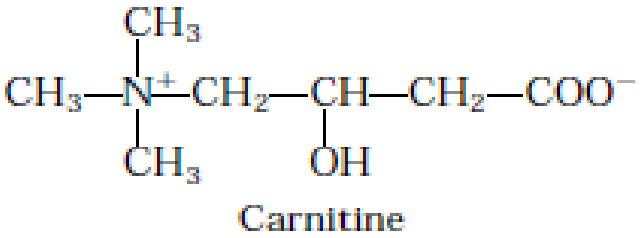


# Conversion of a fatty acid to a fatty acyl–CoA (Activation Step)



# Fatty acid entry into mitochondria via the acyl-carnitine/ carnitine transporter




Carnitine

After fatty acyl–carnitine is formed at the outer membrane or in the intermembrane space, it moves into the matrix by facilitated diffusion through the transporter in the inner membrane. In the matrix, the acyl group is transferred to mitochondrial coenzyme A, freeing carnitine to return to the intermembrane space through the same transporter.

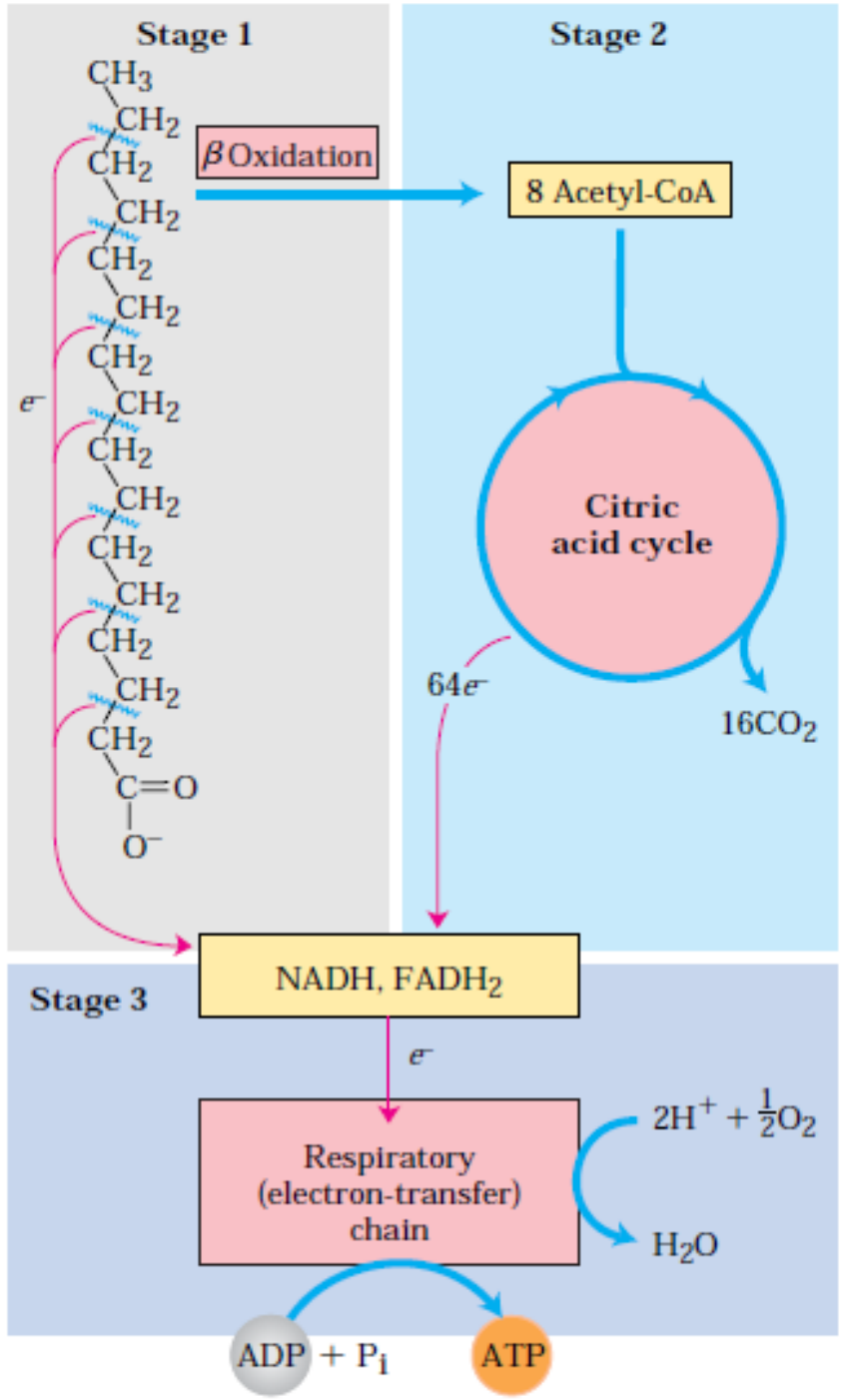
# Summery

- The fatty acids of triacylglycerols furnish a large fraction of the oxidative energy in animals. Dietary triacylglycerols are emulsified in the small intestine by bile salts, hydrolyzed by intestinal lipases, absorbed by intestinal epithelial cells, reconverted into triacylglycerols, then formed into chylomicrons by combination with specific apolipoproteins

- Chylomicrons deliver triacylglycerols to tissues, where lipoprotein lipase releases free fatty acids for entry into cells. Triacylglycerols stored in adipose tissue are mobilized by a hormone-sensitive triacylglycerol lipase. The released fatty acids bind to serum albumin and are carried in the blood to the heart, skeletal muscle, and other tissues that use fatty acids for fuel.

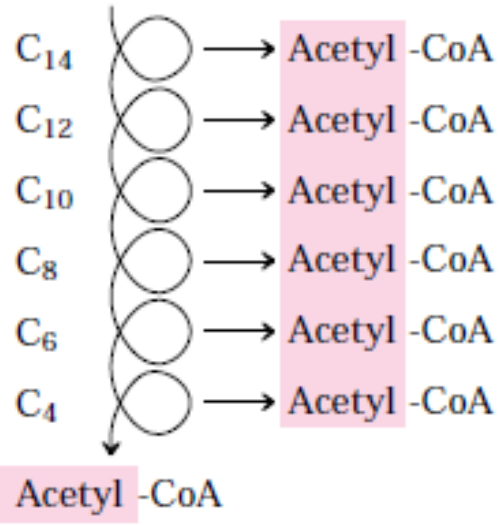
- Once inside cells, fatty acids are activated at the outer mitochondrial membrane by conversion to fatty acyl–CoA thioesters. Fatty acyl–CoA to be oxidized enters mitochondria in three steps, via the carnitine shuttle

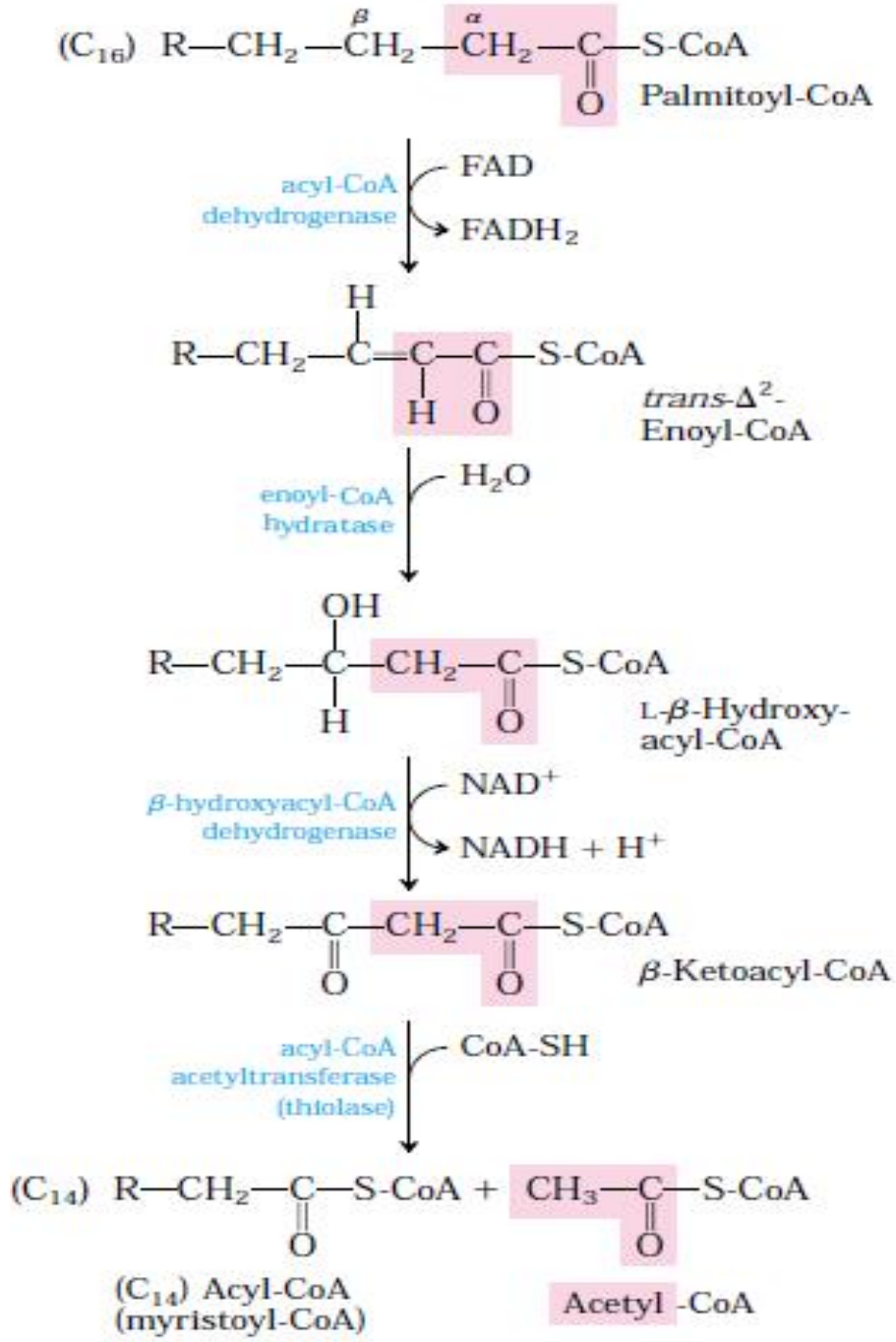
# Stages of fatty acid oxidation



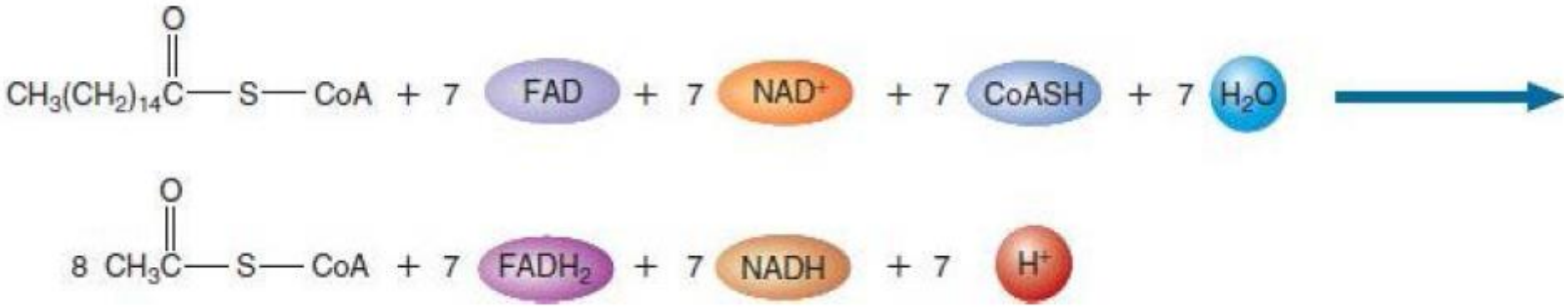
# The -oxidation pathway

- In each pass through this four-step sequence, one acetyl residue (shaded in pink) is removed in the form of acetyl-CoA from the carboxyl end of the fatty acyl chain in this example palmitate (C16), which enters as palmitoyl-CoA
- Six more passes through the pathway yield seven more molecules of acetyl-CoA, the seventh arising from the last two carbon atoms of the 16-carbon chain. Eight molecules of acetyl-CoA are formed in all



# The following equation summarizes the oxidation of palmitoyl-CoA

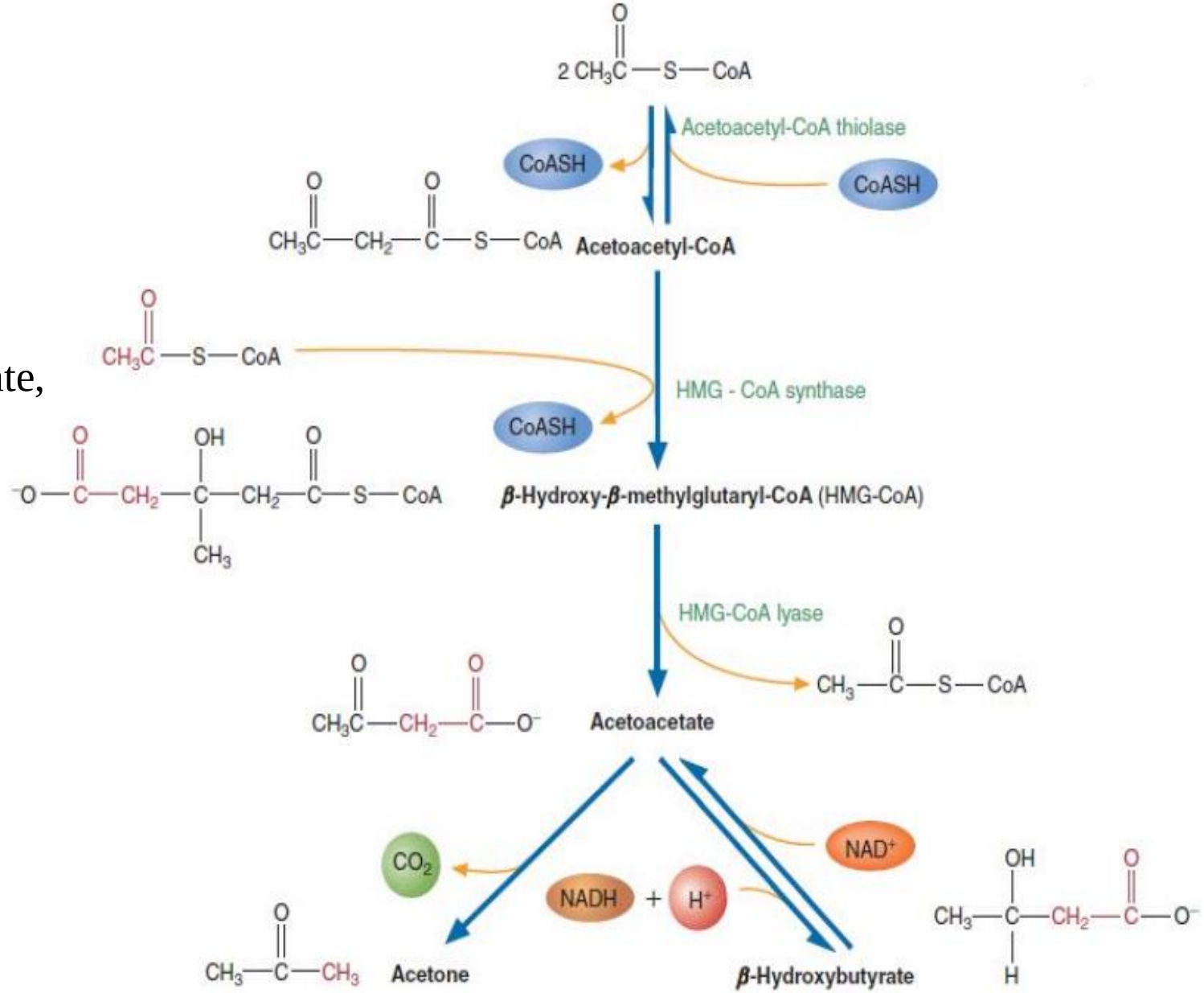


# Lecture 9
# Lipid metabolism II

Dr. Bilal J M Aldahham

# Ketone Body Formation

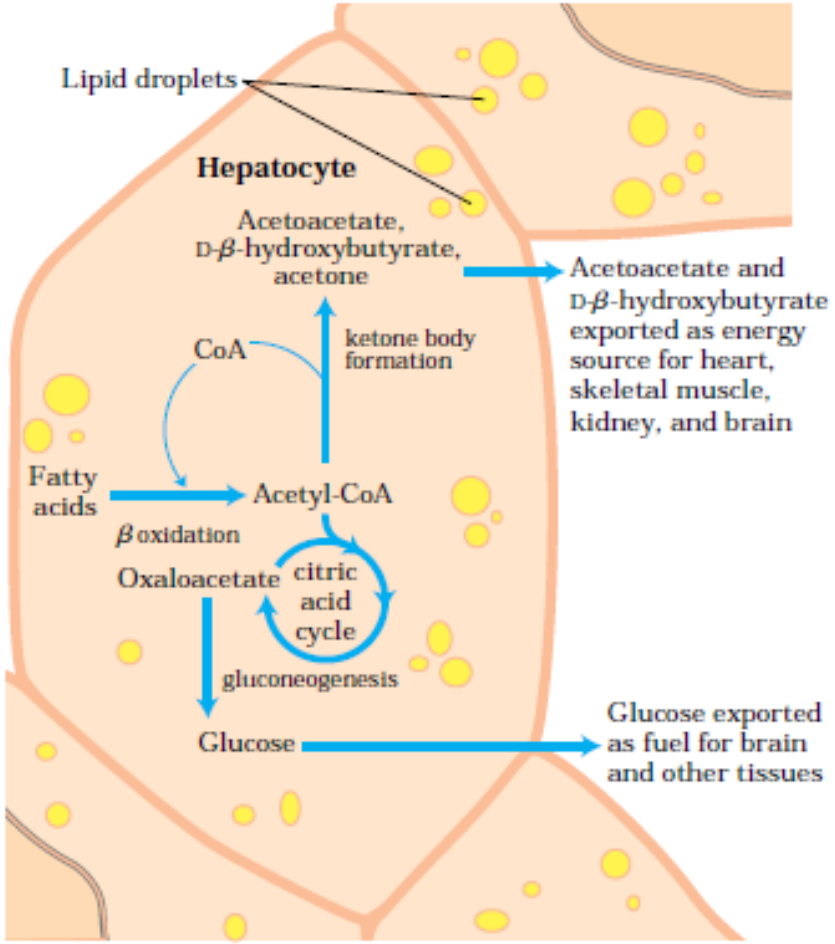
Ketone bodies (acetoacetate, β hydroxybutyrate, and acetone) are produced within liver mitochondria when excess acetyl-CoA is available. Under normal circumstances, only small amounts of ketone bodies are produced



# Ketone body formation and export from the liver

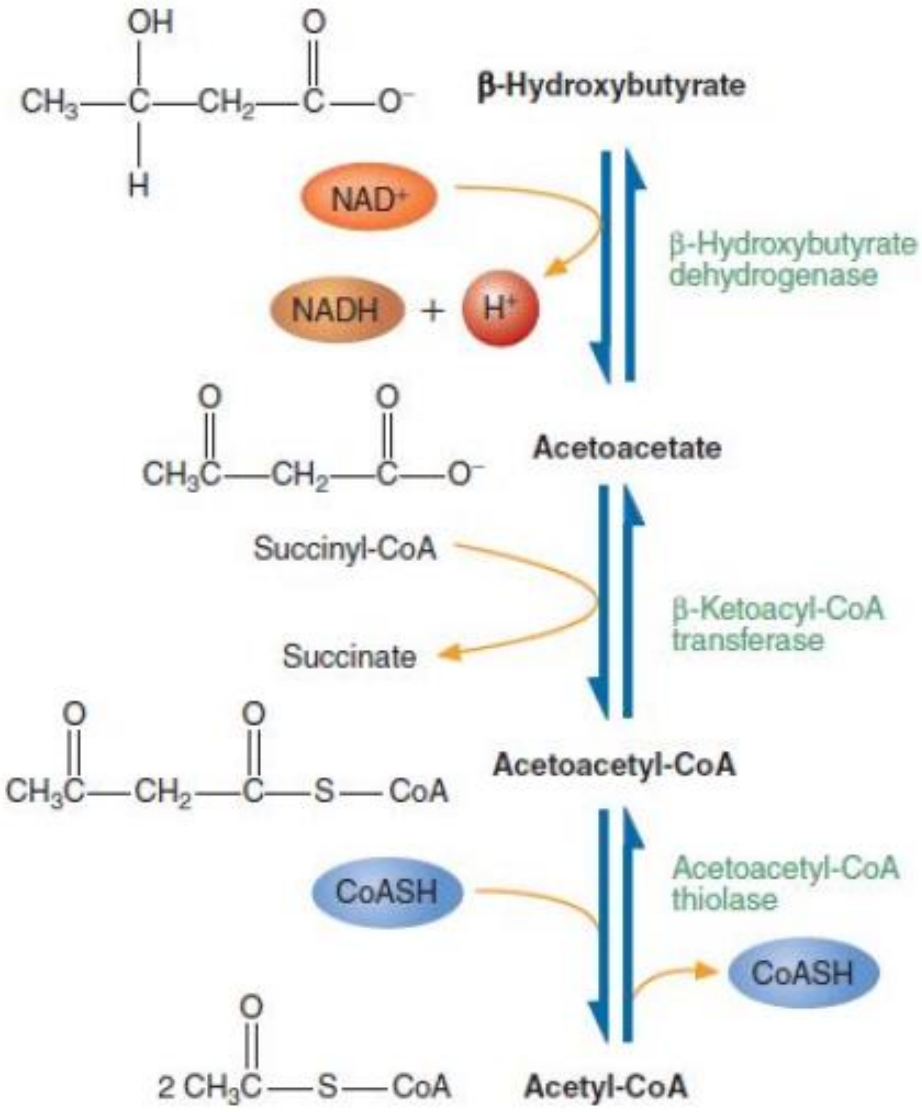
Healthy, well-nourished individuals produce ketone bodies at a relatively low rate. When acetyl-CoA accumulates (as in starvation or untreated diabetes, for example), thiolase catalyzes the condensation of two acetyl-CoA molecules to acetoacetyl-CoA, the parent compound of the three ketone bodies. The reactions of ketone body formation occur in the matrix of liver mitochondria. The six-carbon compound -hydroxy--methylglutaryl-CoA (HMG-CoA) is also an intermediate of sterol biosynthesis, but the enzyme that forms HMG-CoA in that pathway is cytosolic. HMG-CoA lyase is present only in the mitochondrial matrix.

Conditions that promote gluconeogenesis (untreated diabetes, severely reduced food intake) slow the citric acid cycle (by drawing off oxaloacetate) and enhance the conversion of acetyl-CoA to acetoacetate. The released coenzyme A allows continued oxidation of fatty acids



# Conversion of Ketone Bodies to Acetyl-CoA

Some organs (e.g., heart and skeletal muscle) can use ketone bodies (β-hydroxybutyrate and acetoacetate) as an energy source under normal conditions. During starvation, however, ketone bodies become an important fuel source for the brain. Because liver does not have β-ketoacid-CoA transferase, it cannot use ketone bodies as an energy source. These reactions are reversible. The energy yield from the catabolism of β-hydroxybutyrate, 21.5 ATPs, is calculated as follows. Two acetyl CoA products yield 20 ATPs in the citric acid cycle, electron transport, and oxidative phosphorylation. An additional NADH, produced by the oxidation of β-hydroxybutyrate to form acetoacetate, yields 2.5 ATPs. Because of the activation of acetoacetate by succinyl CoA, one ATP equivalent is subtracted from the sum of 22.5 ATPs thereby yielding 21.5 ATPs



# Summery of Ketone bodies

- The ketone bodies—acetone, acetoacetate, and β-hydroxybutyrate—are formed in the liver. The latter two compounds serve as fuel molecules in extrahepatic tissues, through oxidation to acetyl-CoA and entry into the citric acid cycle.

- Overproduction of ketone bodies in uncontrolled diabetes or severely reduced calorie intake can lead to acidosis or ketosis.

# Types of Lipases in the Human Body

- Lipases are the enzymes which degrades triacylglycerol and release free fatty acids. The lipases are: 1. lingual lipase, in mouth ( it is not very important in lipid metabolism) 2. gastric lipase, gastric lipase starts to break down triacylglycerols into diglycerides and fatty acids in stomach. 3. pancreatic lipase, secreted by pancreatic acinar cells, complete fat digestion in the proximal small intestine. 4. lipoprotein lipase, Lipoprotein lipase plays a critical role in breaking down fat in the form of triglycerides, which are carried from various organs to the blood by molecules called lipoproteins. 5. hormone sensitive lipase, hydrolyze either a fatty acid from a triacylglycerol molecule, freeing a fatty acid and diglyceride, or a fatty acid from a diacylglycerol molecule, freeing a fatty acid and monoglyceride in adipose tissue. 6. hepatic lipase, 7. adipose tissue lipoprotein lipase LPL, hydrolyze TriAcylGlycerol from lipoprotein in the adipose tissue.

# LIPID BIOSYNTHESIS

- They are the principal form of stored energy in most organisms and major constituents of cellular membranes. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, and phosphatidylinositol).

- Biosynthesis of Fatty Acids and Eicosanoids
- Biosynthesis of Triacylglycerols
- Biosynthesis of Membrane Phospholipids
- Biosynthesis of Cholesterol, Steroids, and Isoprenoids

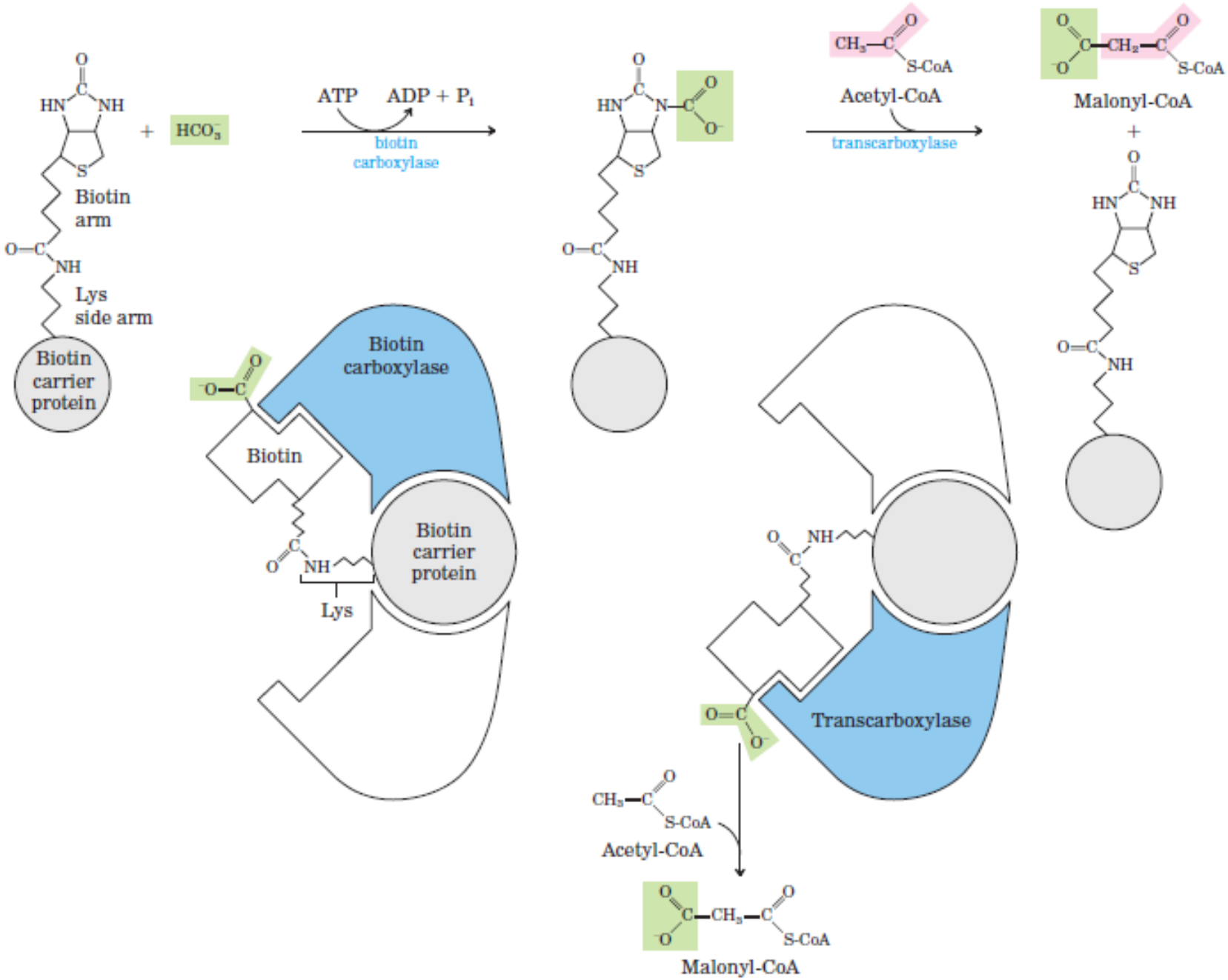
We are going to explain the red colored pathways.

# Biosynthesis of Fatty Acids

- First important step is

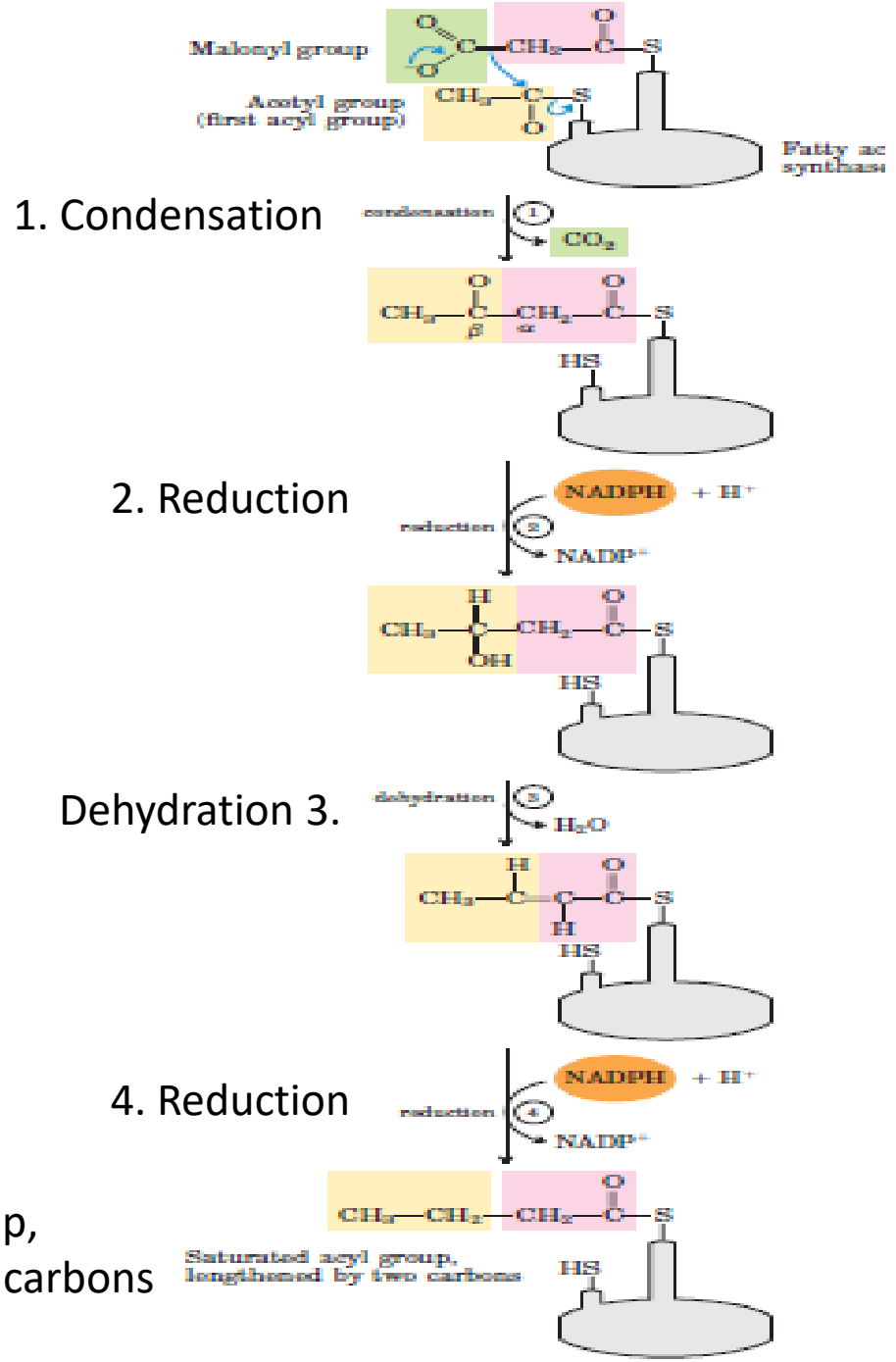
**Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate.**

- The formation of malonyl-CoA from acetyl-CoA is an irreversible process, catalyzed by **acetyl-CoA carboxylase.**
- in animal cells, all three activities are part of a single multifunctional polypeptide.

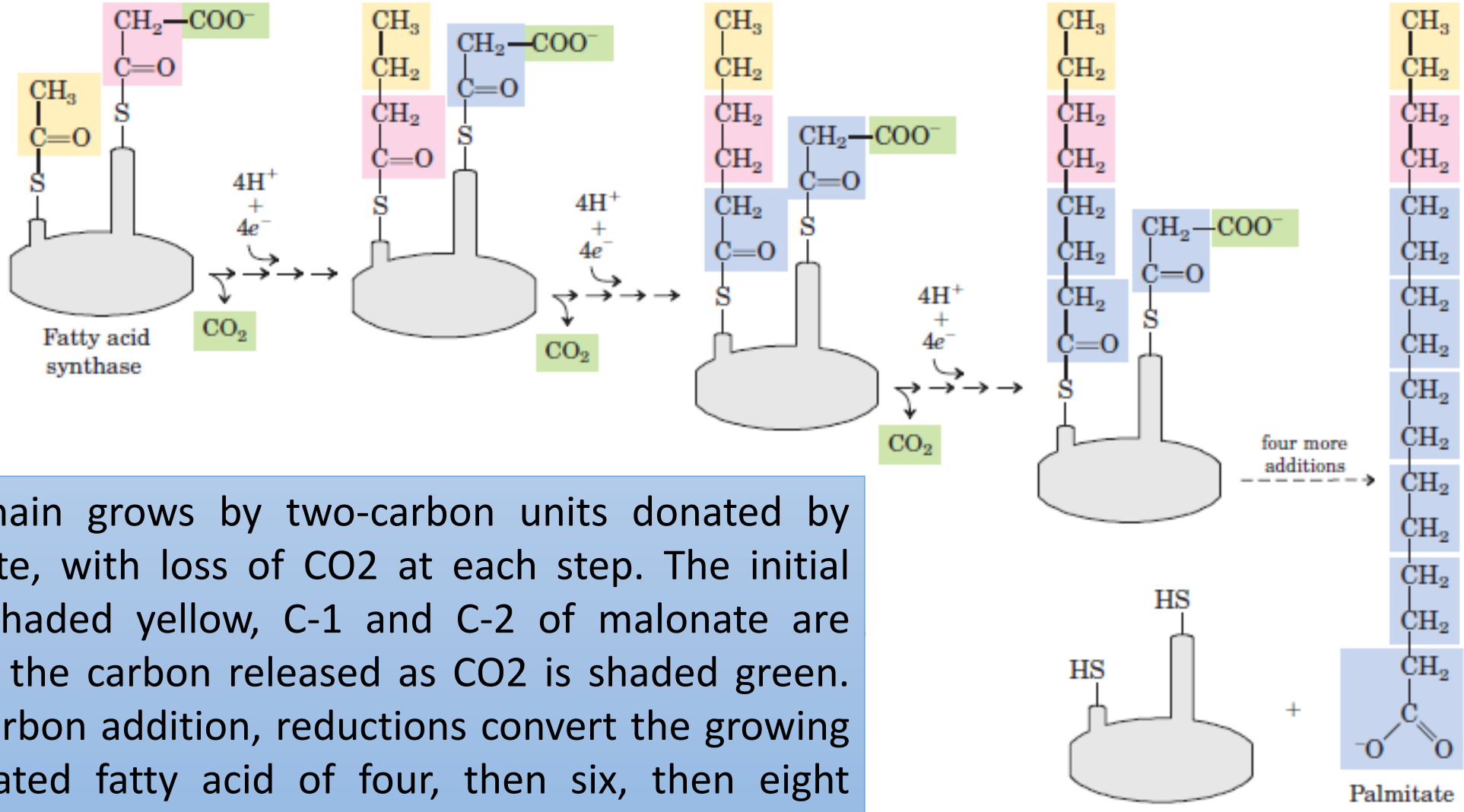


# Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence

- Addition of two carbons to a growing fatty acyl chain: a four-step sequence.

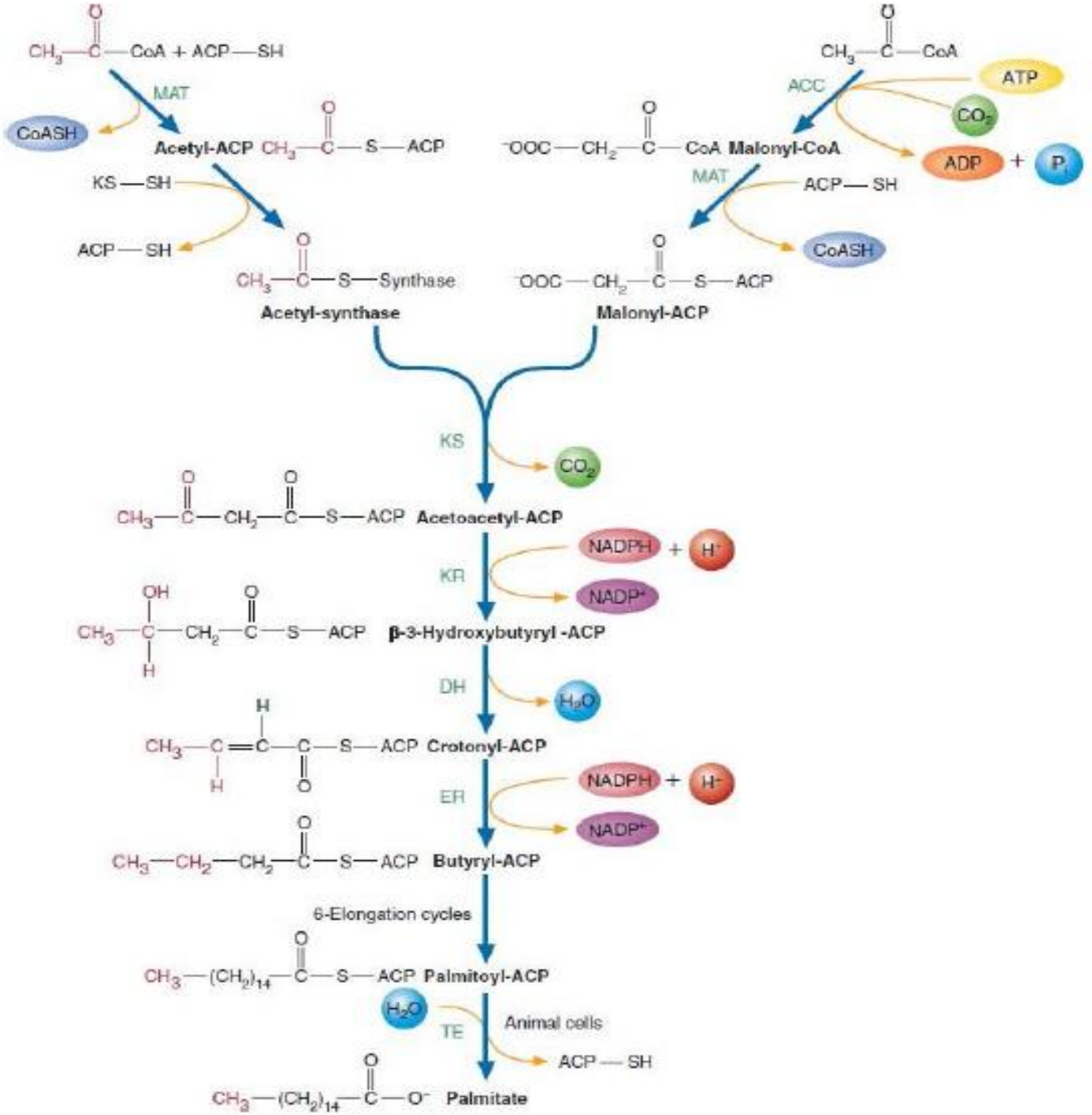


# The overall process of palmitate synthesis




The fatty acyl chain grows by two-carbon units donated by activated malonate, with loss of CO2 at each step. The initial acetyl group is shaded yellow, C-1 and C-2 of malonate are shaded pink, and the carbon released as CO2 is shaded green. After each two carbon addition, reductions convert the growing chain to a saturated fatty acid of four, then six, then eight carbons, and so on. The final product is palmitate (16:0).

# Overall steps of Palmitate Biosynthesis



# Energy consuming of Palmitate biosynthesis

- We can consider the overall reaction for the synthesis of palmitate from acetyl-CoA in two parts. First, the formation of seven malonyl-CoA molecules:

  7 Acetyl-CoA+ 7CO2 + 7ATP $\longrightarrow$ 7 malonyl-CoA + 7ADP + 7$P_i$

- then seven cycles of condensation and reduction:

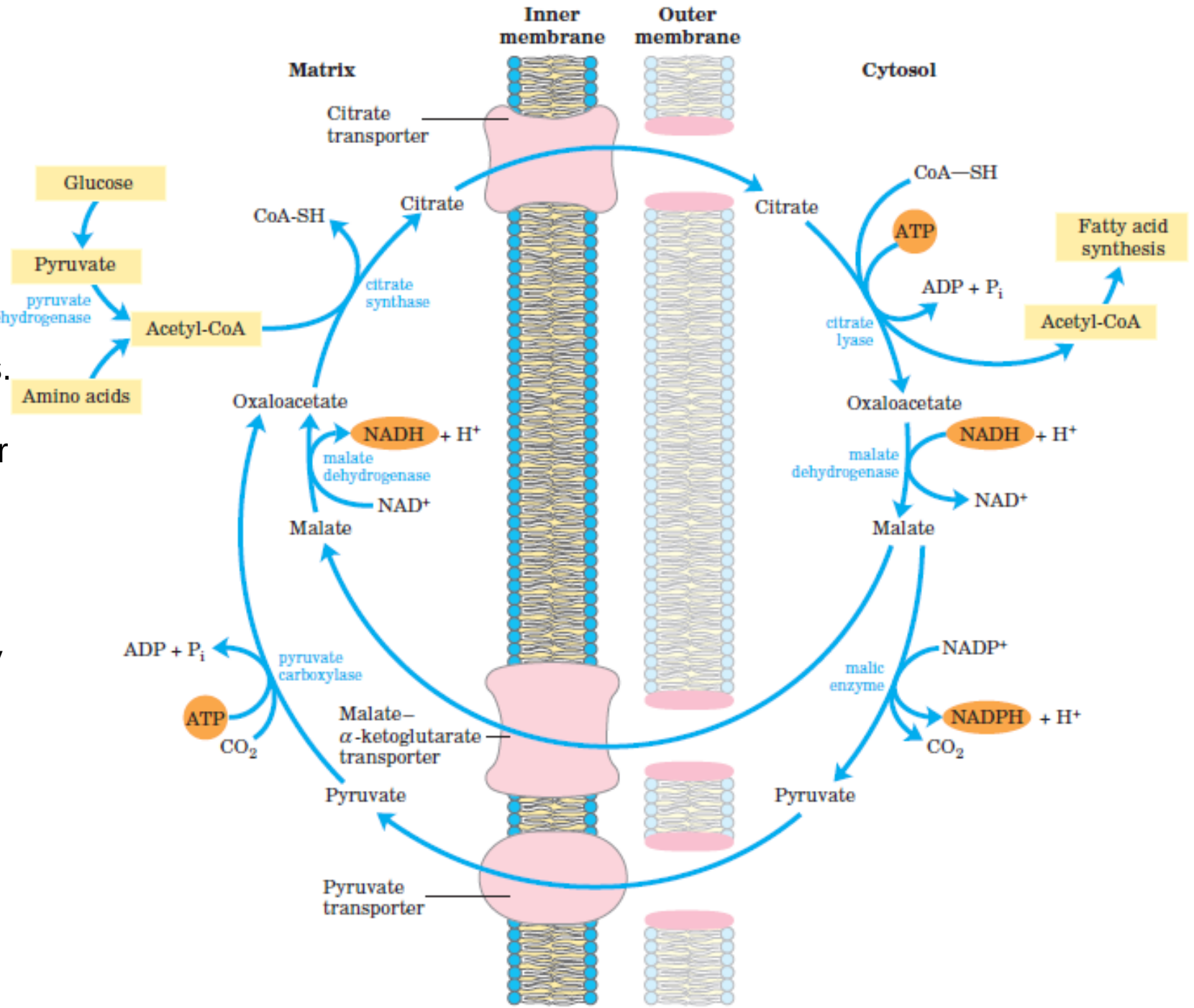
Acetyl-CoA +7 malonyl-CoA +14NADPH +14$H^+$ $\longrightarrow$ palmitate+ 7$CO_2$ +8 CoA + 14$NADP^+$ 6$H_2O$

- The overall process (the sum of Eqns 1 and 2) is:

8 Acetyl-CoA + 7ATP + 14NADPH + 14$H^+$ $\longrightarrow$ palmitate + 8 CoA + 7ADP + 7$P_i$ 14$NADP^+$ + 6$H_2O$

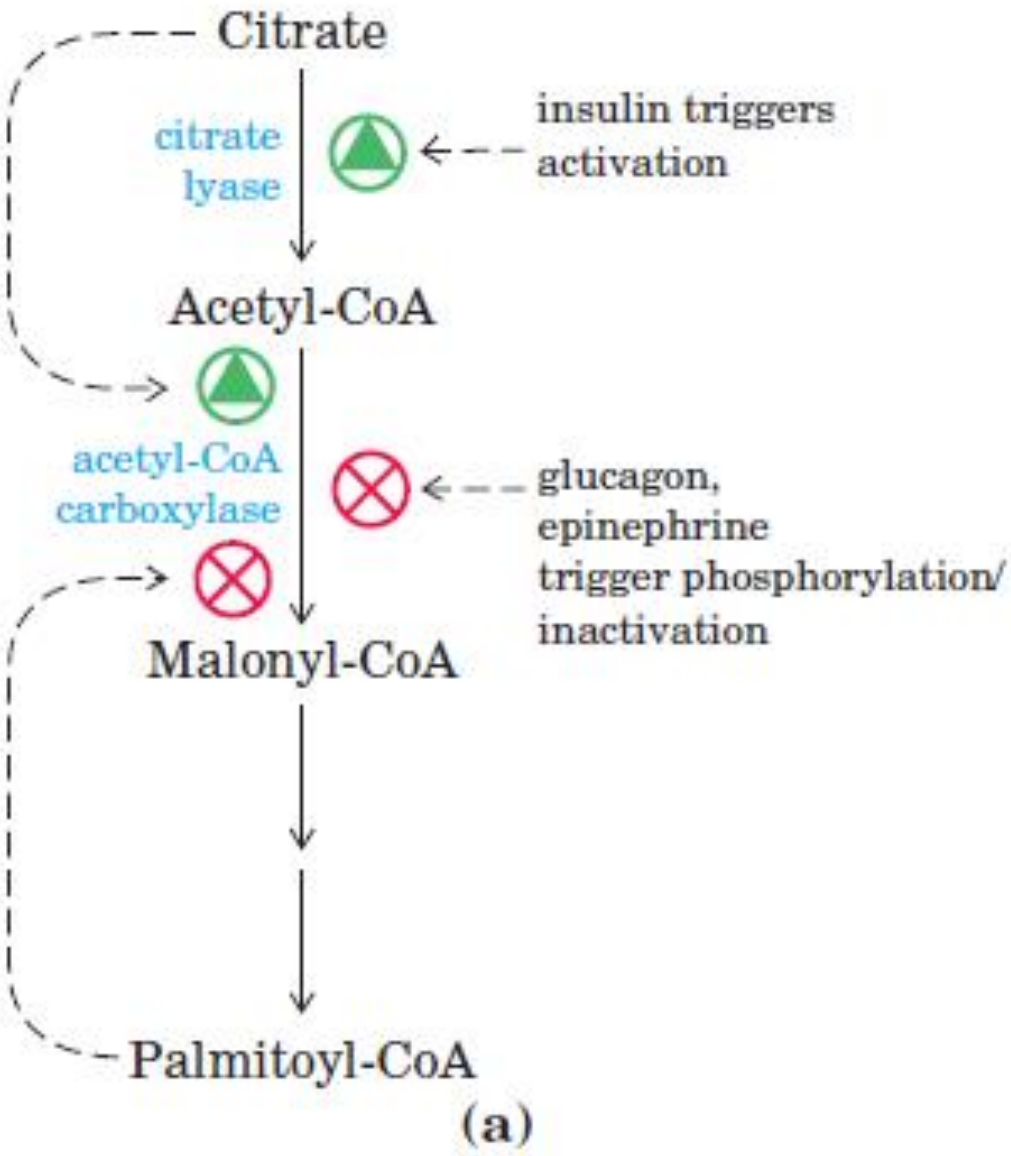
# Shuttle for transfer of acetyl groups from mitochondria to the cytosol

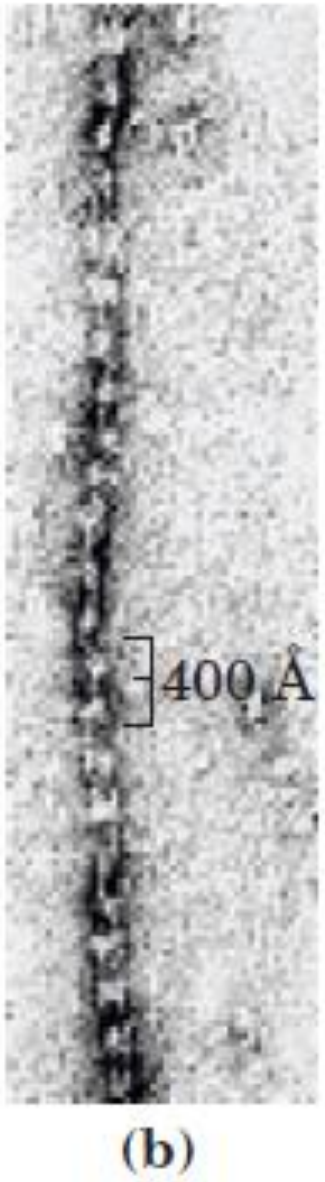
The mitochondrial outer membrane is freely permeable to all these compounds. Pyruvate derived from amino acid catabolism in the mitochondrial matrix, or from glucose by glycolysis in the cytosol, is converted to acetyl CoA in the matrix. Acetyl groups pass out of the mitochondrion as citrate; in the cytosol they are delivered as acetyl-CoA for fatty acid synthesis. Oxaloacetate is reduced to malate, which returns to the mitochondrial matrix and is converted to oxaloacetate. An alternative fate for cytosolic malate is oxidation by malic enzyme to generate cytosolic NADPH; the pyruvate produced returns to the mitochondrial matrix.



# Regulation of fatty acid synthesis

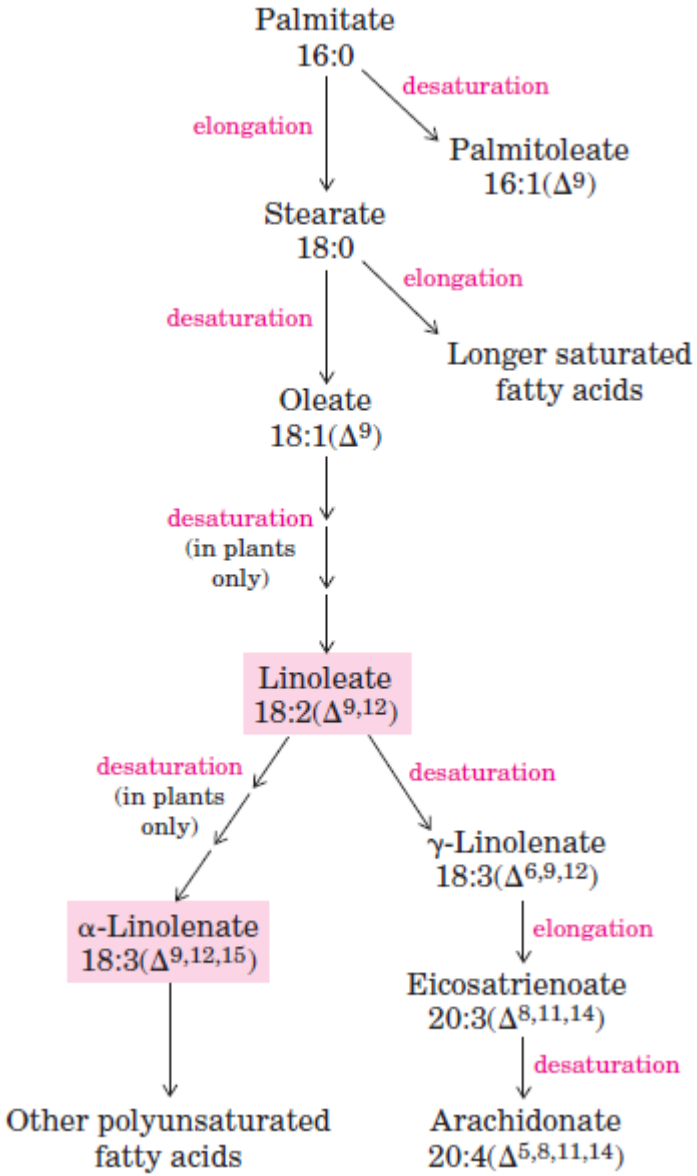
**(a)** In the cells of vertebrates, both allosteric regulation and hormone dependent covalent modification influence the flow of precursors into malonyl CoA.
**(b)** Filaments of acetyl-CoA carboxylase (the active, dephosphorylated form) as seen with the electron microscope.



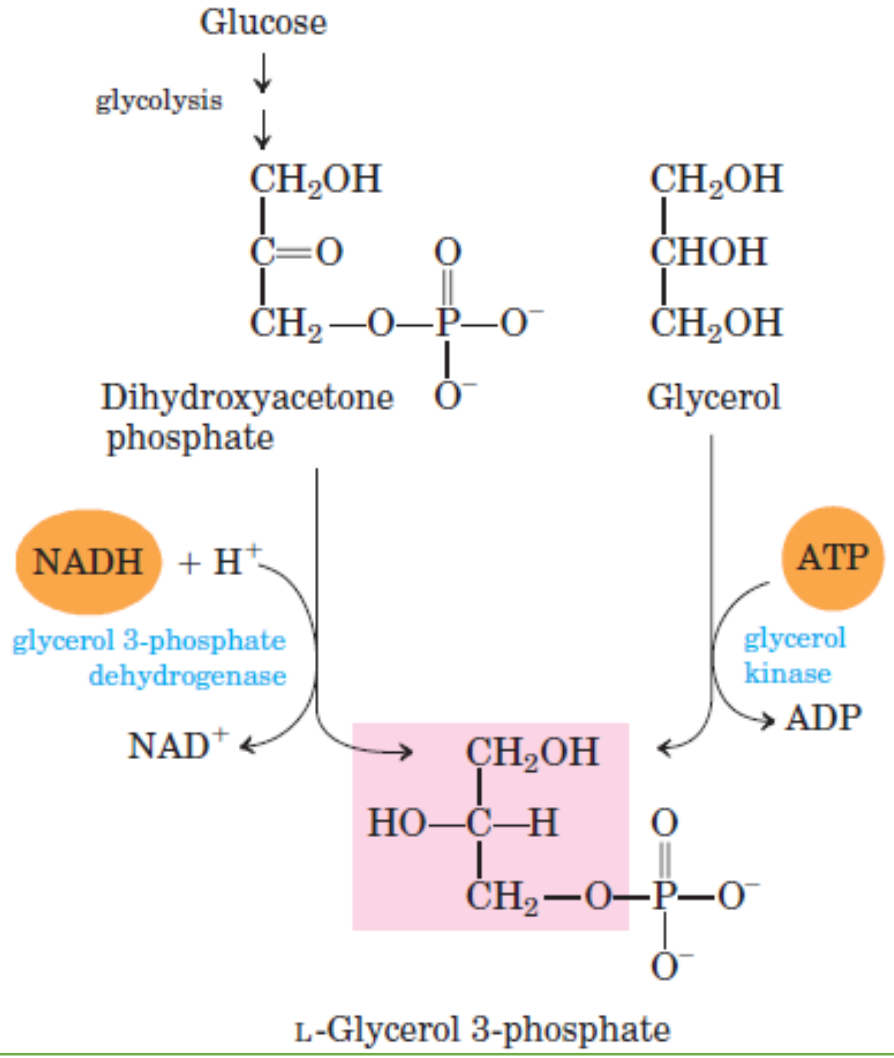



# للاطلاع

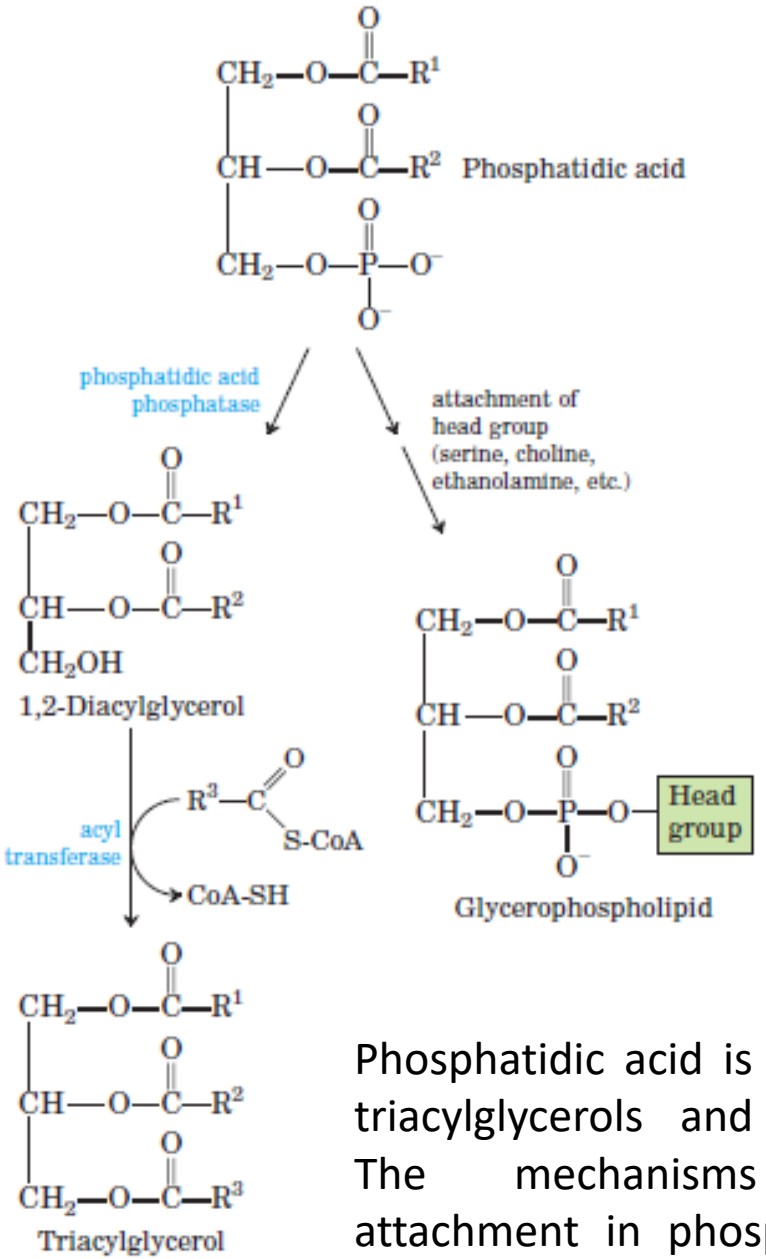
- لمعرفة أهمية الحامض الدهني palmitate اذ ان كثير من الاحماض الدهنية يتم تخليقها منه بتفاعلات جانبية اضافية



# Biosynthesis of Triacylglycerols

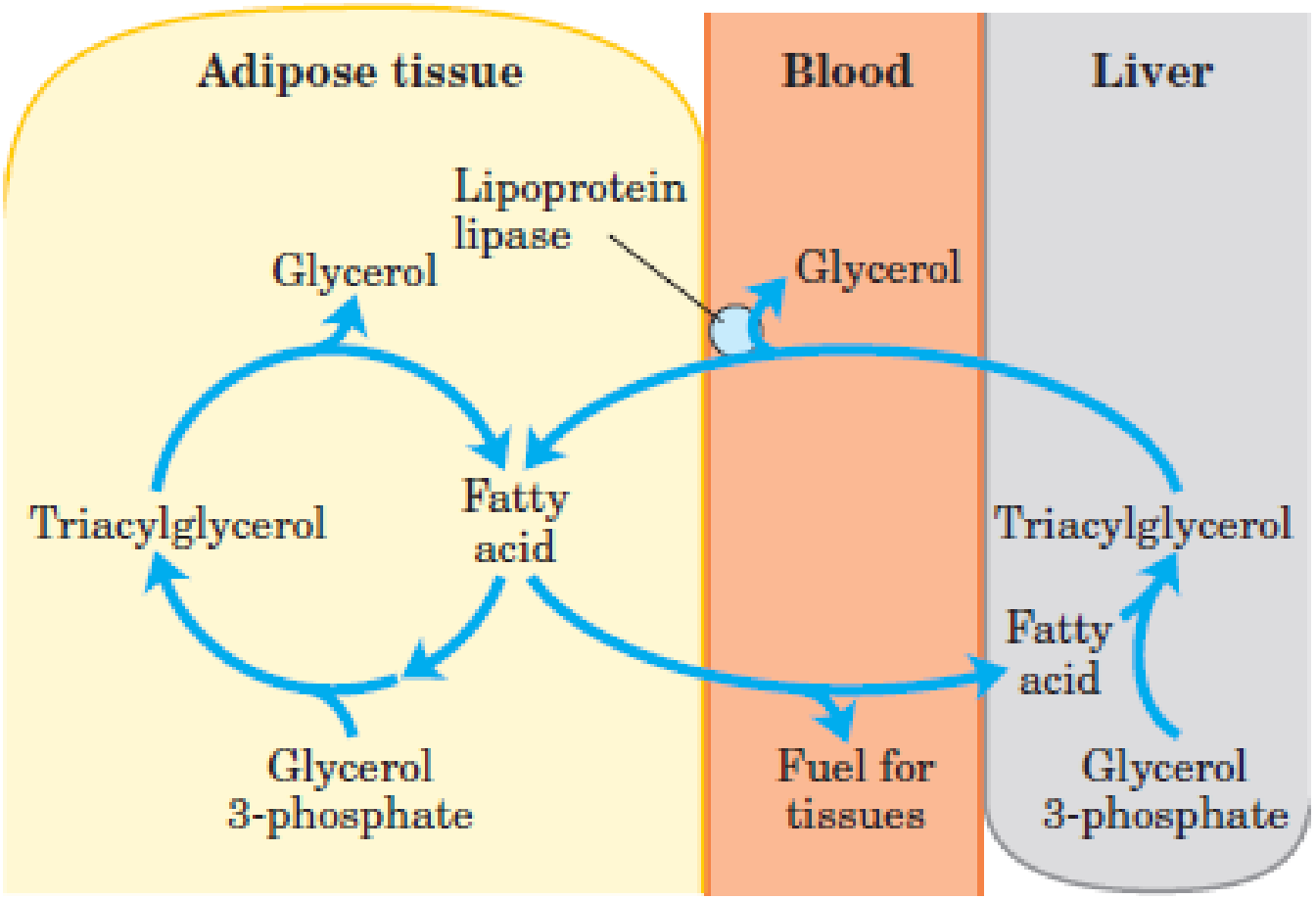



Then several steps to convert Glycerol 3-phosphate to phosphatidic acid, the precursor of TAG.

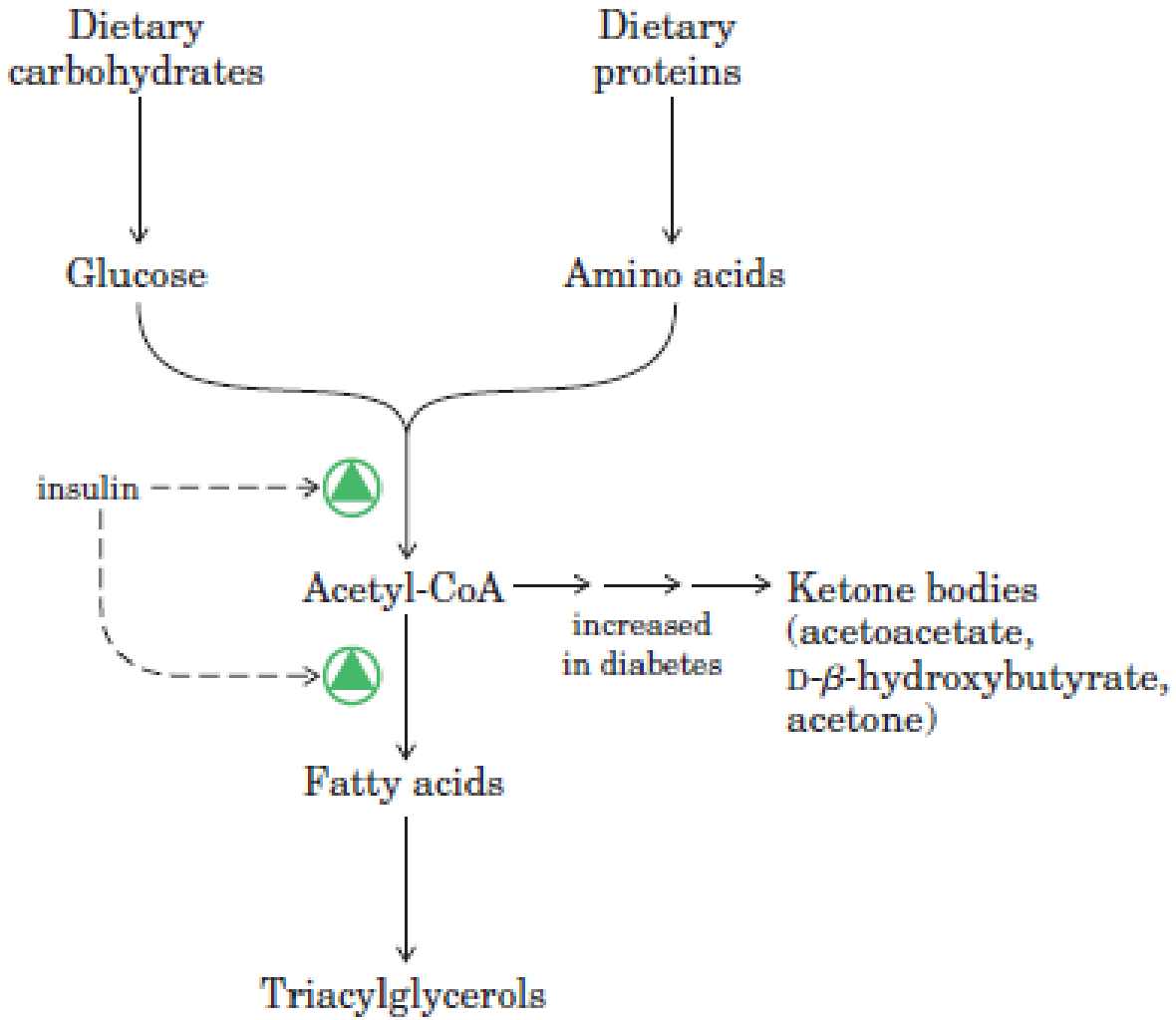



Phosphatidic acid is the precursor of both triacylglycerols and glycerophospholipids. The mechanisms for head-group attachment in phospholipid synthesis are described later in this section

# The triacylglycerol cycle

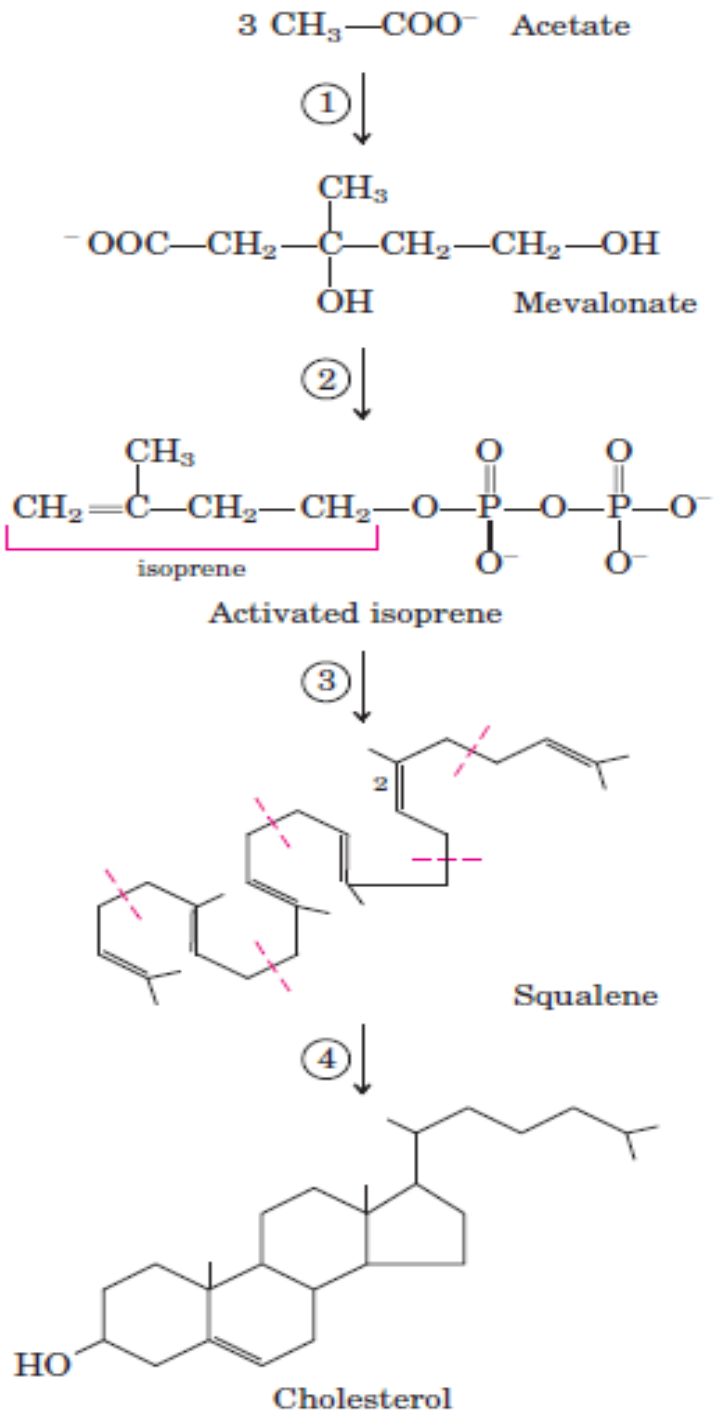


# Regulation of triacylglycerol synthesis by insulin



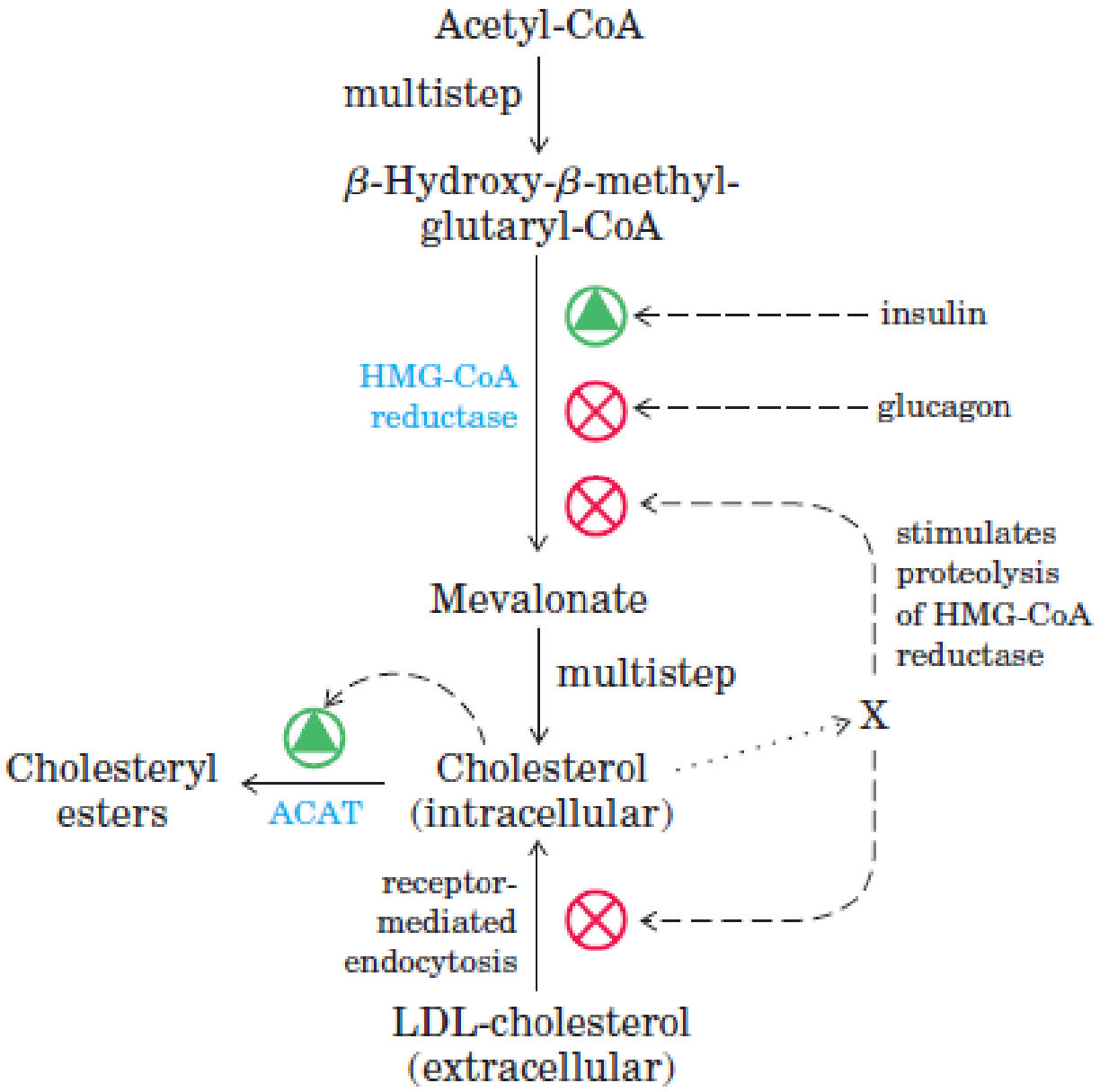
# Summary of cholesterol biosynthesis

- Stage 1 Synthesis of Mevalonate from Acetate
- Stage 2 Conversion of Mevalonate to Two Activated Isoprenes
- Condensation of Six Activated Isoprene Units to Form Squalene
- Conversion of Squalene to the Four-Ring Steroid Nucleus

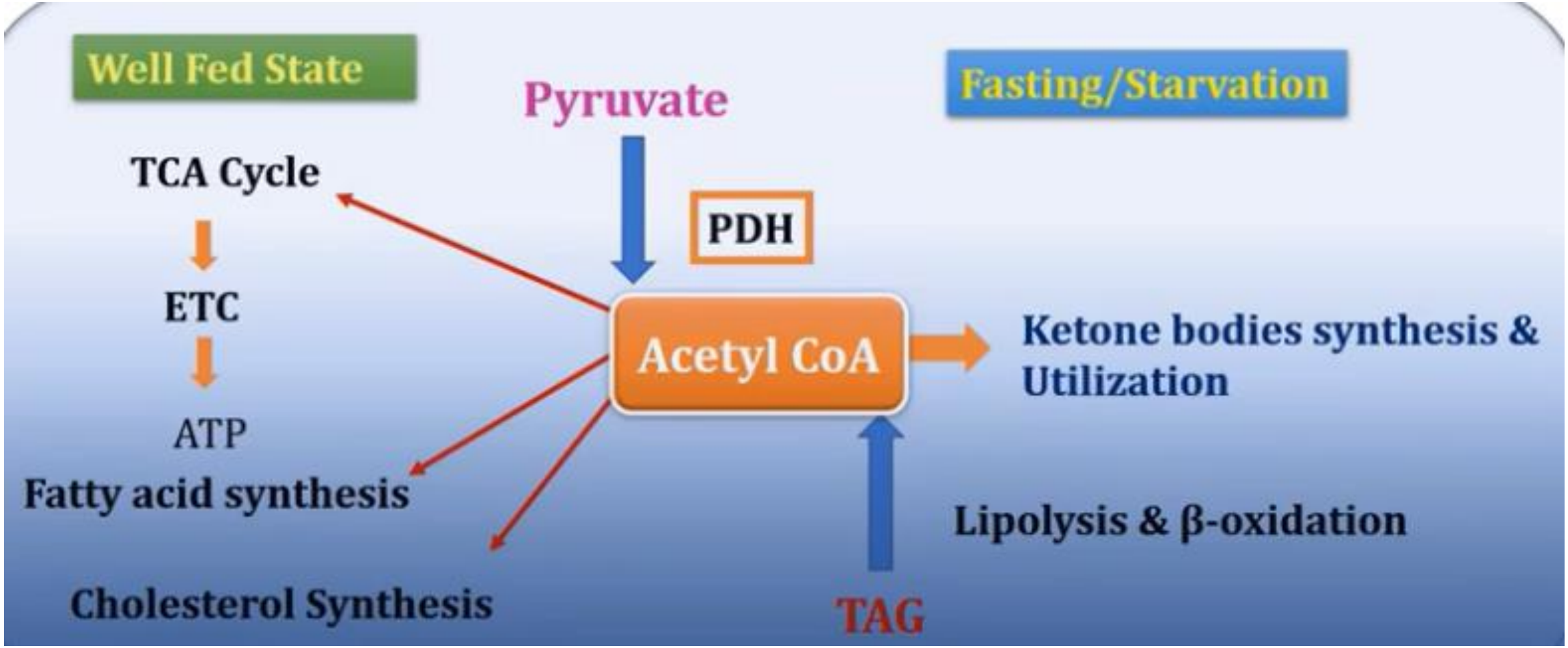


# Regulation of cholesterol formation balances synthesis with dietary uptake

- Glucagon promotes phosphorylation (inactivation) of HMG-CoA reductase; insulin promotes dephosphorylation (activation). X represents unidentified metabolites of cholesterol that stimulate proteolysis of HMG-CoA reductase



# Overview of Lipid Metabolism



# Major metabolic pathways

## Fed state

- Digestion & absorption of lipids
- Fatty acid synthesis(De novo)
- TAG Synthesis & storage
- Lipoprotein metabolism
- Cholesterol synthesis
- Compound lipid synthesis (Phospholipids, Glycolipids)

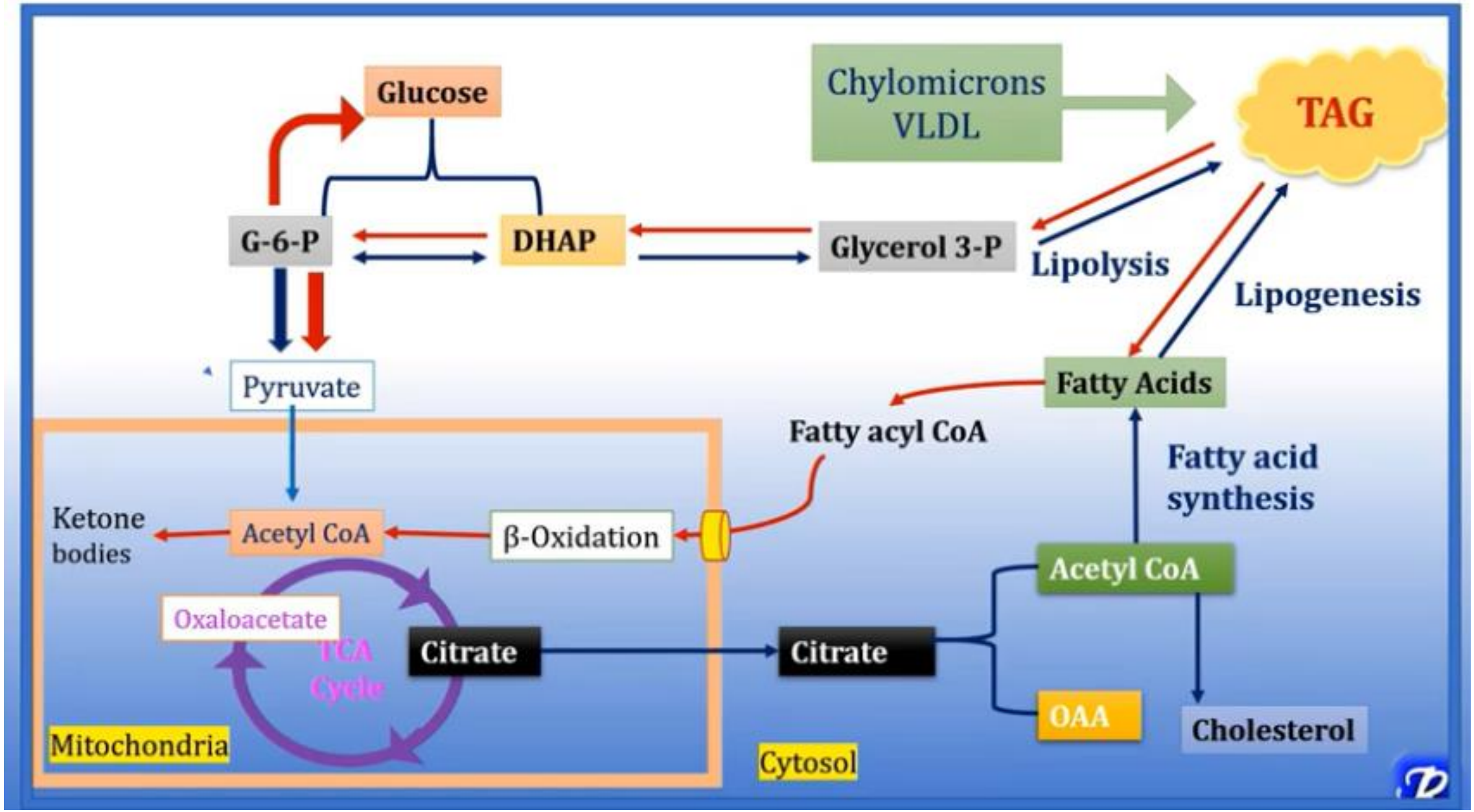
**Insulin**

## Fasting & Starvation

- Lipolysis(TAG breakdown)
- FA oxidation
- Ketone body synthesis & utilisation

**Glucagon/Epinephrine**

# Relations of Carbohydrates and Lipids metabolism

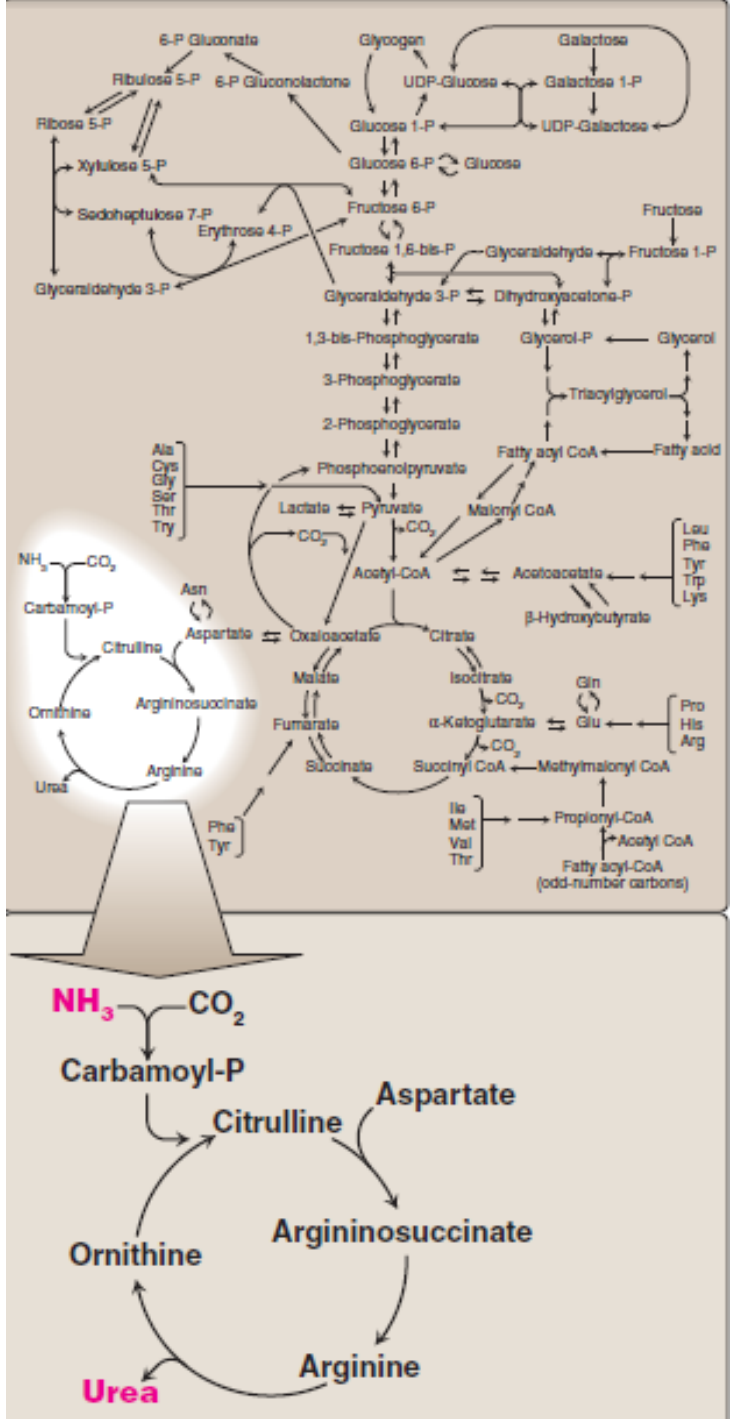


# Lecture 8
# Protein Metabolism

Dr. Bilal J M Aldahham

# Overview

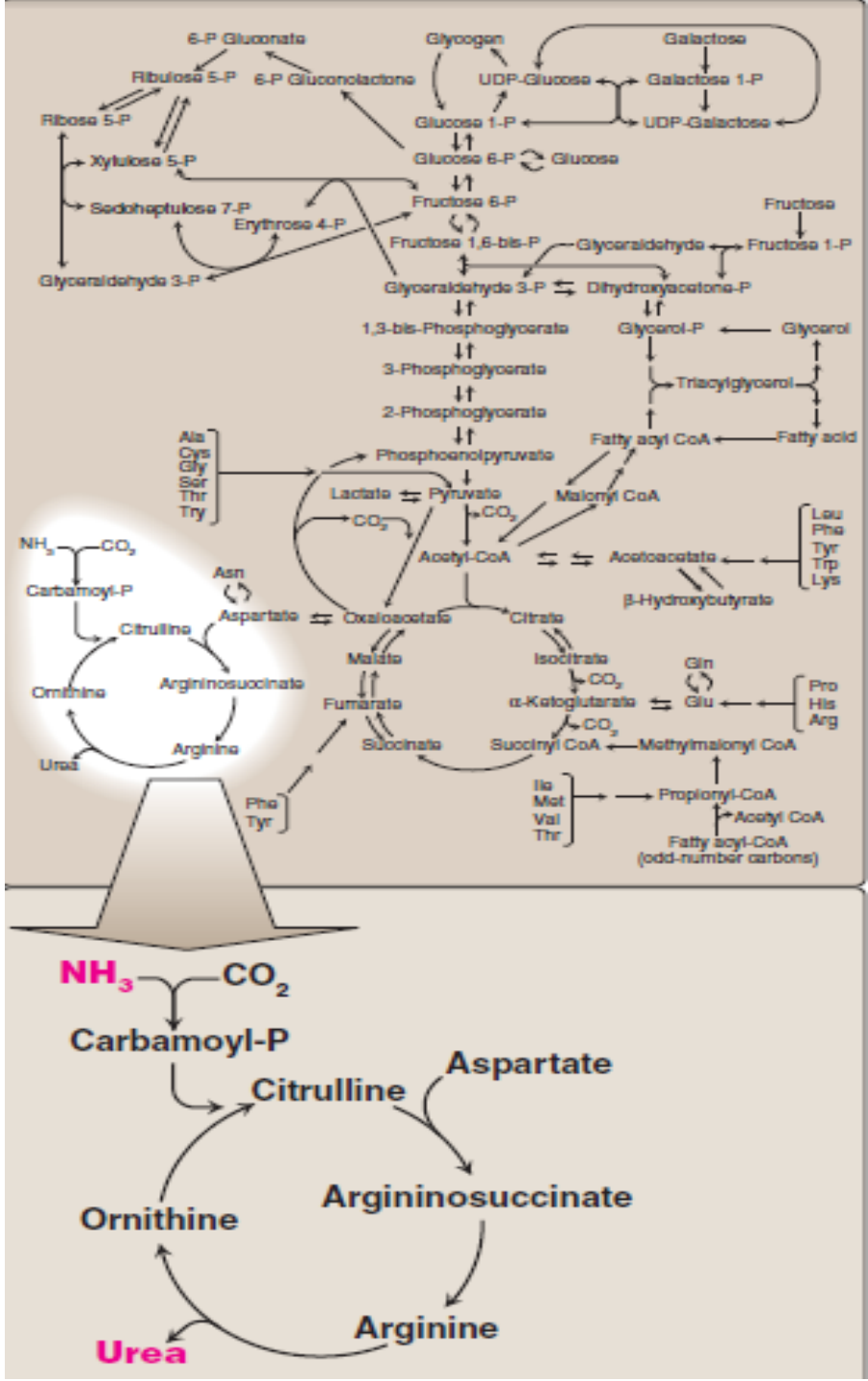
- Unlike fats and carbohydrates, amino acids are not stored by the body, that is, no protein exists whose sole function is to maintain a supply of amino acids for future use.
- Therefore, amino acids must be obtained from the diet, synthesized de novo, or produced from normal protein degradation.
- Any amino acids in excess of the biosynthetic needs of the cell are rapidly degraded.
- The first phase of catabolism involves the removal of the α -amino groups (usually by transamination and subsequent oxidative deamination), forming ammonia and the corresponding α-keto acid—the “carbon skeletons” of amino acids.



# Overview

- A portion of the free ammonia is excreted in the urine, but most is used in the synthesis of urea, which is quantitatively the most important route for disposing of nitrogen from the body.

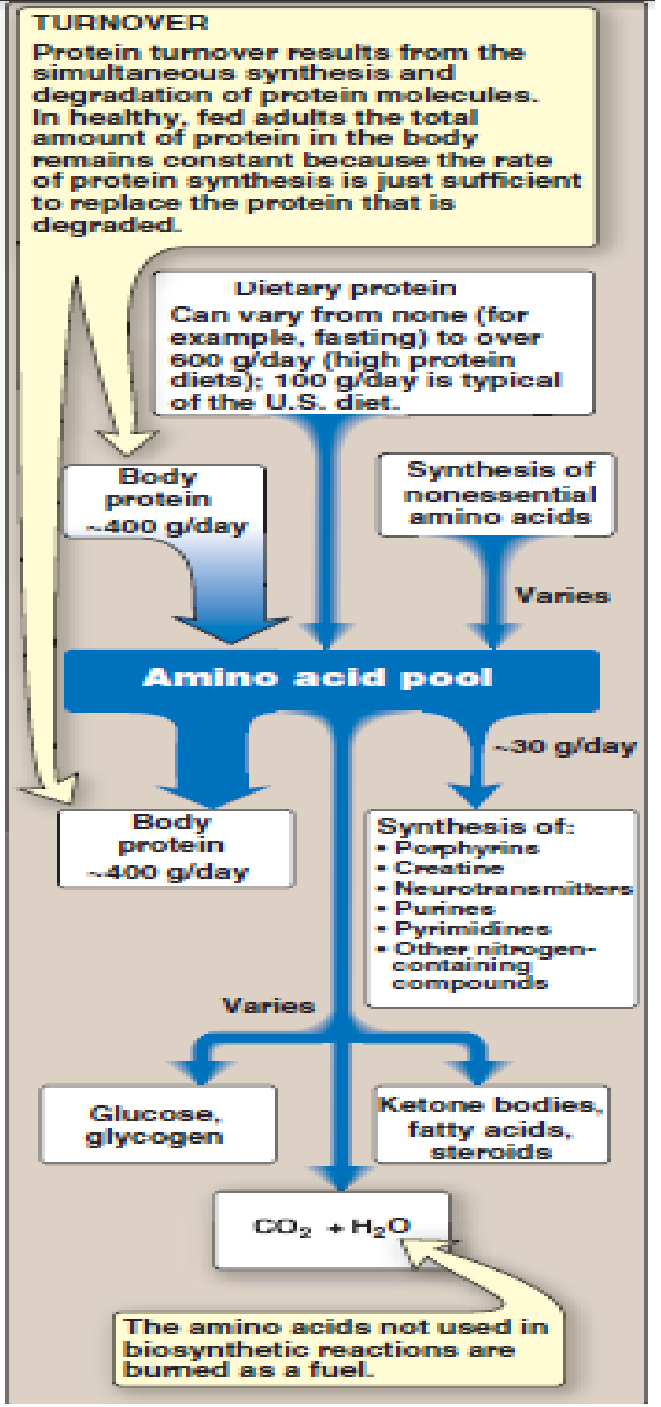
- In the second phase of amino acid catabolism, described in Chapter 20, the carbon skeletons of the α -ketoacids are converted to common intermediates of energy producing, metabolic pathways. These compounds can be metabolized to $CO_2$ and water, glucose, fatty acids, or ketone bodies by the central pathways of metabolism.



# Source and Fate of amino acids

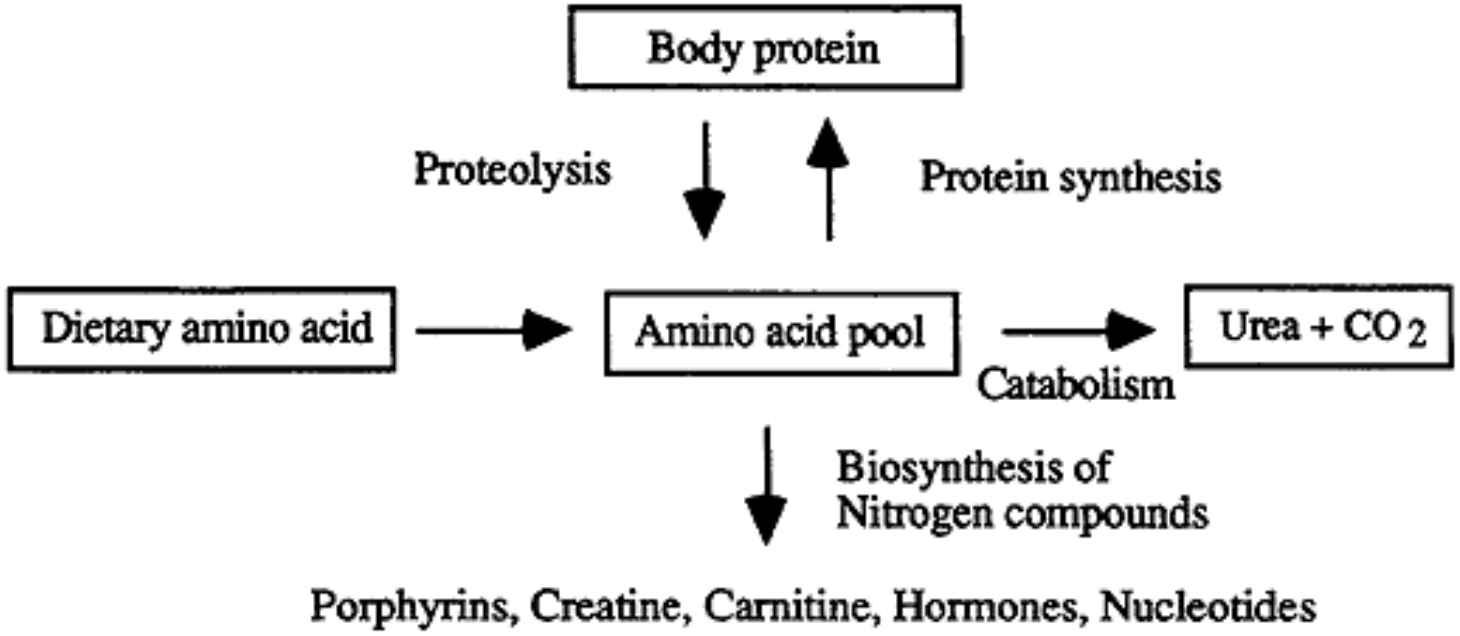
- Free amino acids are present throughout the body, for example, in cells, blood, and the extracellular fluids. For the purpose of this discussion, envision all these amino acids as if they belonged to a single entity, called the amino acid pool.
- This pool is supplied by three sources: 1) amino acids provided by the degradation of body proteins, 2) amino acids derived from dietary protein, and 3) synthesis of nonessential amino acids from simple intermediates of metabolism.
- Conversely, the amino pool is depleted by three routes: 1) synthesis of body protein, 2) amino acids consumed as precursors of essential nitrogen-containing small molecules, and 3) conversion of amino acids to glucose, glycogen, fatty acids, ketone bodies, or $CO_2 + H_2O$

In healthy, well-fed individuals, the input to the amino acid pool is balanced by the output, that is, the amount of amino acids contained in the pool is constant. The amino acid pool is said to be in a steady state, and the individual is said to be in nitrogen balance.

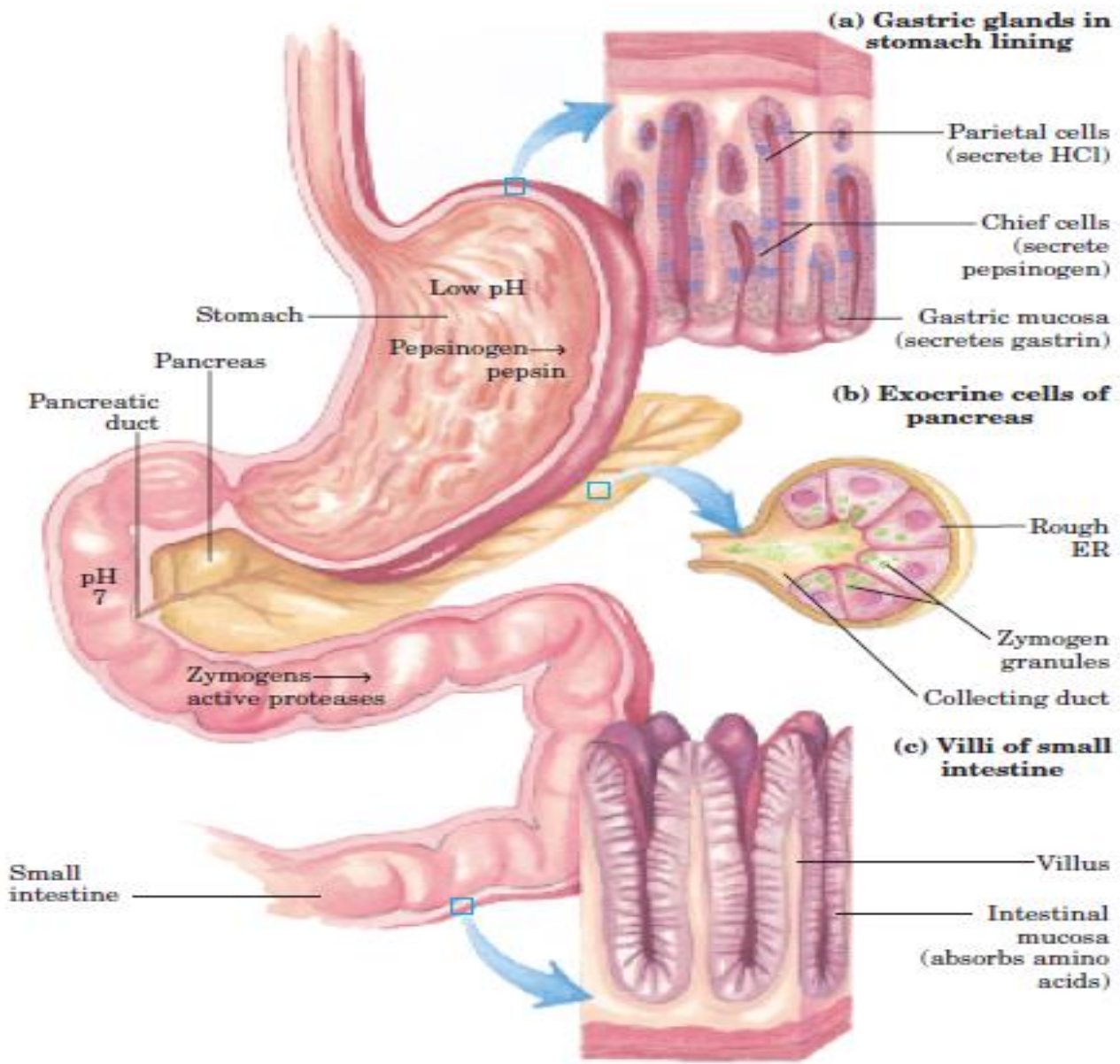


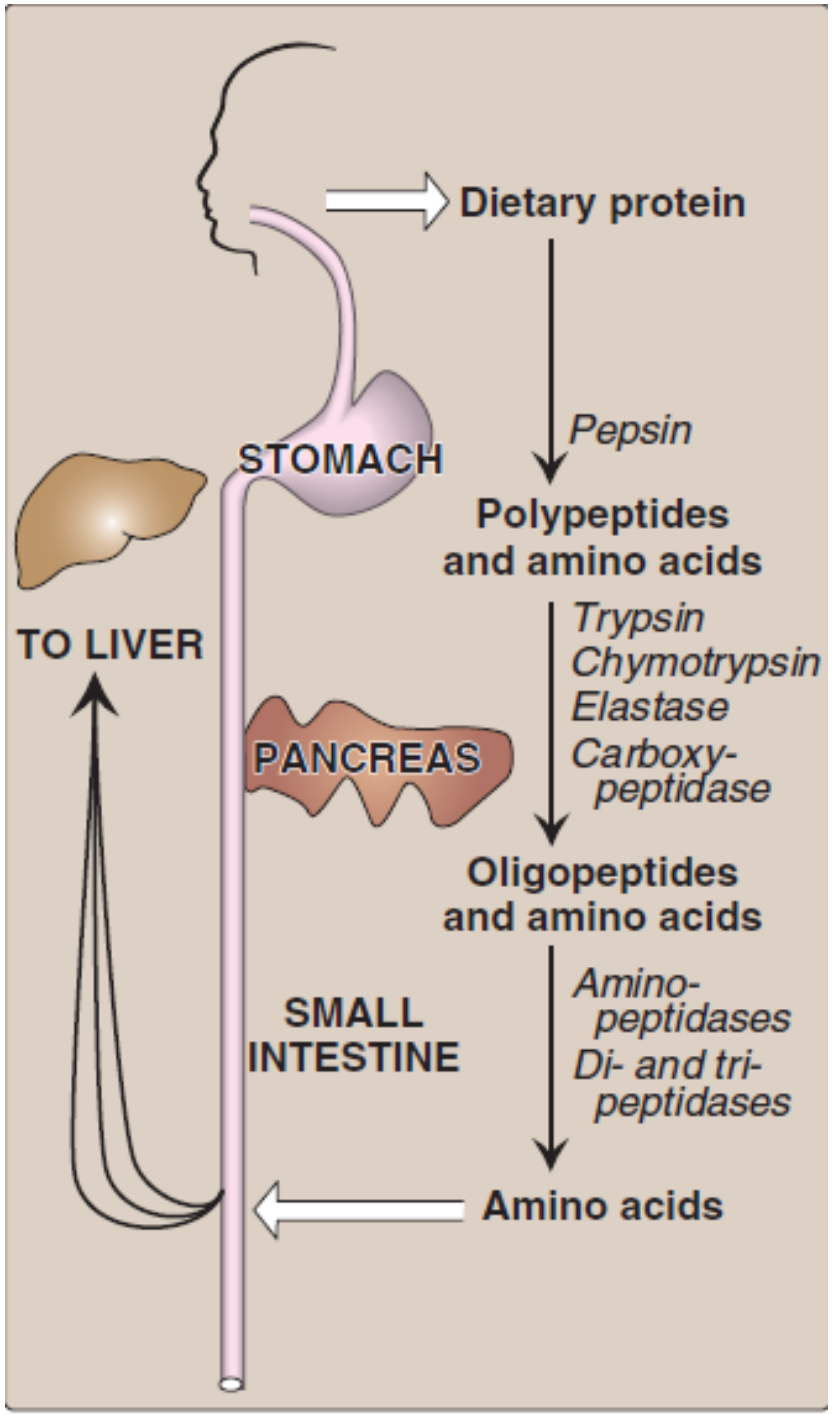
# Protein turnover

- Protein turnover refers to the continual renewal or replacement of protein. It is defined by the balance between protein synthesis and protein degradation. During periods of steady state, the overall rate of protein synthesis is equal to the rate of protein degradation.



# Digestion of dietary proteins by the proteolytic enzymes of the gastrointestinal tract.



# DIGESTION OF PROTEINS

The dietary proteins are denatured on cooking and therefore more easily digested. All these enzymes are hydrolases (class 3 enzymes) in nature. Proteolytic enzymes are secreted as inactive **zymogens** which are converted to their active form in the intestinal lumen. This would prevent autodigestion of the secretory acini. The proteolytic enzymes include:

**Endopeptidases:** They act on peptide bonds inside the protein molecule, so that the protein becomes successively smaller and smaller units. This group includes Pepsin, Trypsin, Chymotrypsin and Elastase.

**Exopeptidases:** Which act only on the peptide bond located at the ends of the polypeptide chain. This group includes:

a. **Carboxypeptidase,** which acts only on the peptide bond at the carboxy terminal end of the chain.

b. **Aminopeptidase,** which acts only on the peptide bond at the amino terminal end of the chain.

# Action of proteolytic enzymes

**TABLE 15.1: Action of proteolytic enzymes**

| Enzyme | Hydrolysis of bonds formed by carboxyl groups of |
|---|---|
| Pepsin | Phe, Tyr, Trp, Met |
| Trypsin | Arg, Lys |
| Chymotrypsin | Phe, Tyr, Trp, Val, Leu |
| Elastase | Ala, Gly, Ser |
| Carboxypeptidase A | C-terminal aromatic amino acid |
| Carboxypeptidase B | C-terminal basic amino acid |

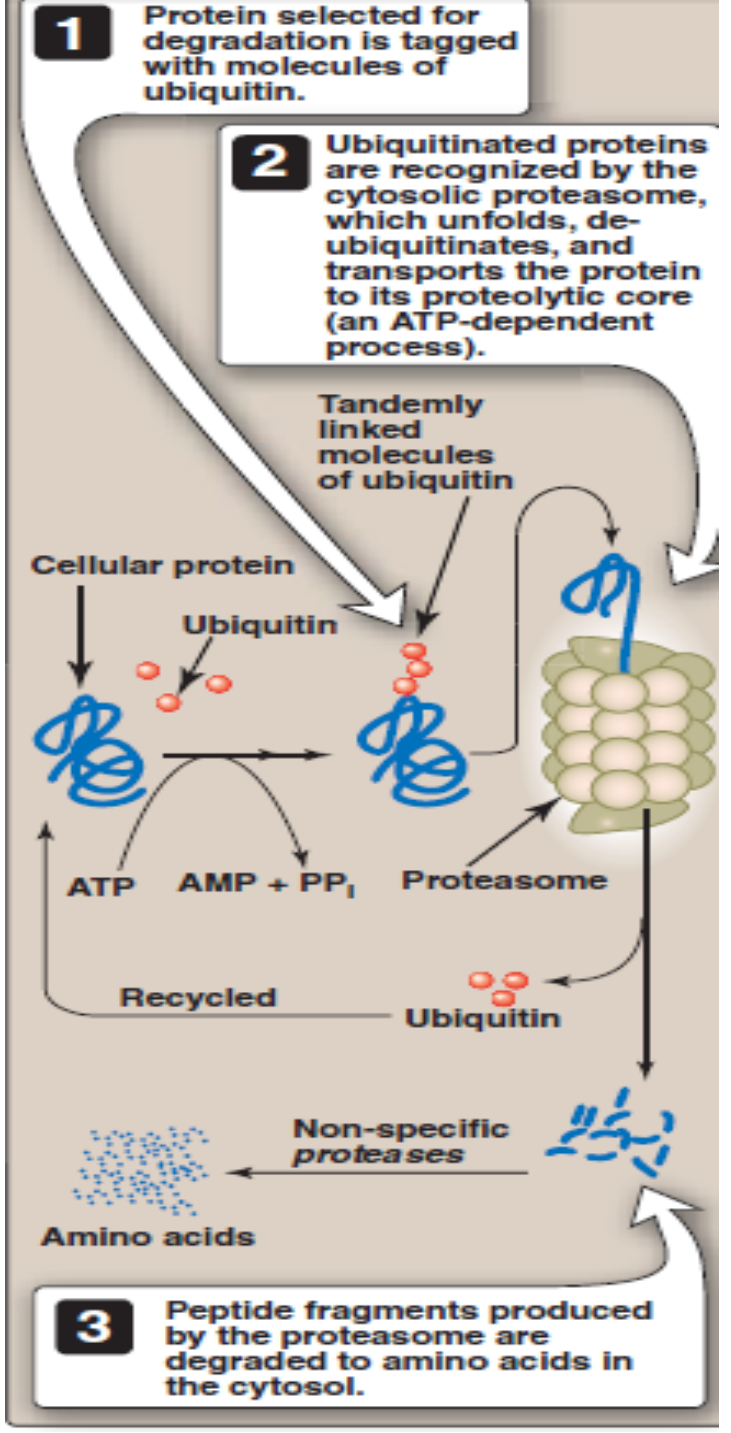
# Food Allergy

Dipeptides and tripeptides can enter the brush border of mucosal cells;

they are immediately hydrolyzed into single amino acids. They are then transported into portal vein. Rarely, larger molecules may pass paracellularly (between epithelial cells) and enter blood stream. These are immunogenic, causing antibody reaction, leading to food allergy.

# The ubiquitin-proteasome degradation pathway of proteins

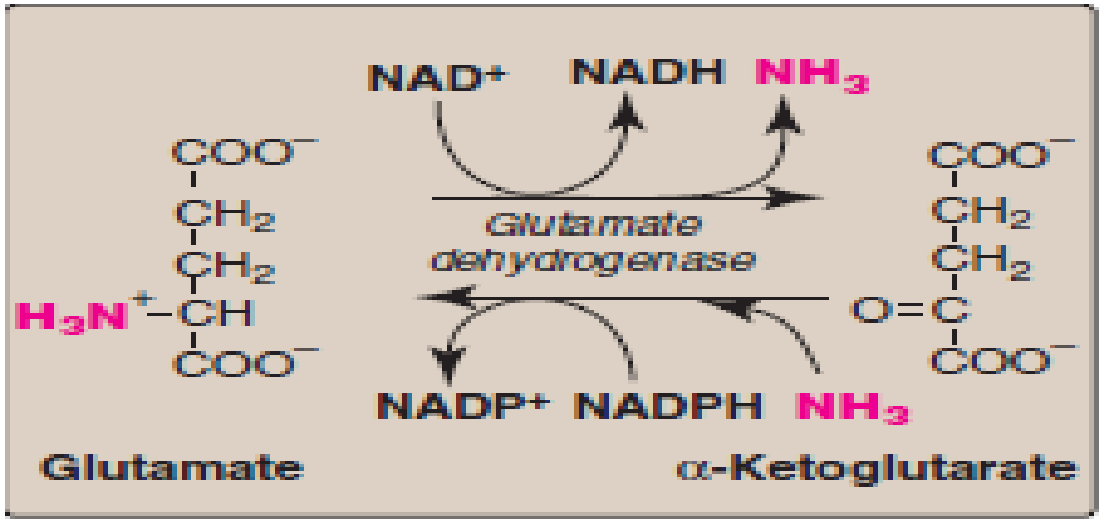
- Proteins selected for degradation by the ubiquitin-proteasome system are first covalently attached to ubiquitin, a small, globular, non-enzymic protein.
- Proteins tagged with ubiquitin are then recognized by a large, barrel-shaped, macromolecular, proteolytic complex called a proteasome, which functions like a garbage disposal
- The proteasome unfolds, deubiquitinates, and cuts the target protein into fragments that are then further degraded to amino acids, which enter the amino acid pool.
- It is noteworthy that the selective degradation of proteins by the ubiquitin-proteasome complex (unlike simple hydrolysis by proteolytic enzymes) requires energy in the form of ATP.

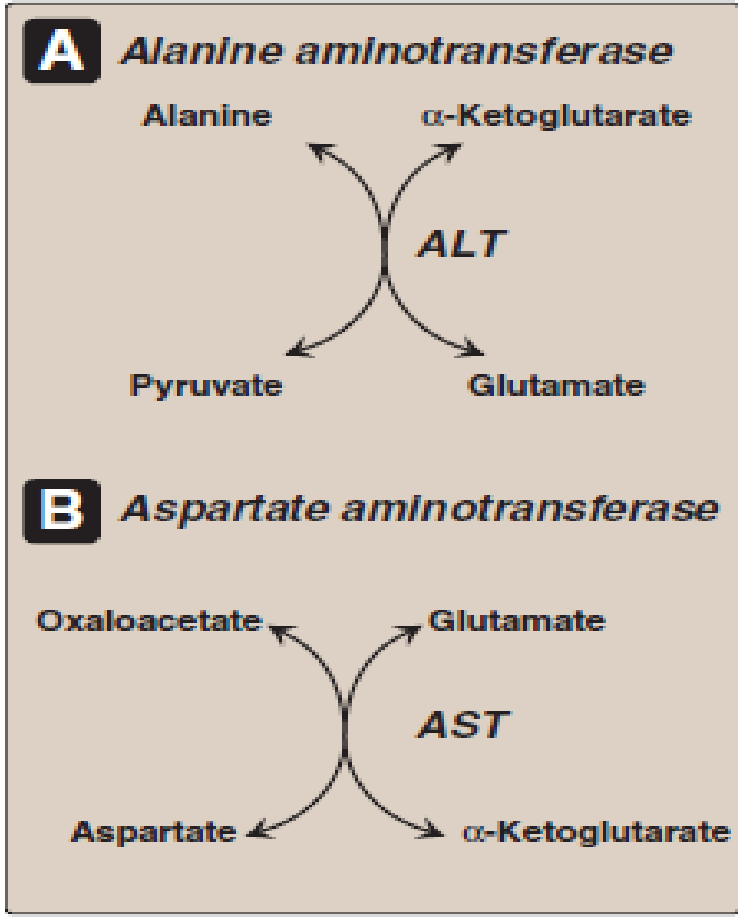


# REMOVAL OF NITROGEN FROM AMINO ACIDS

- A. Transamination: the funneling of amino groups to glutamate

- B. Glutamate dehydrogenase: the oxidative deamination of amino acids



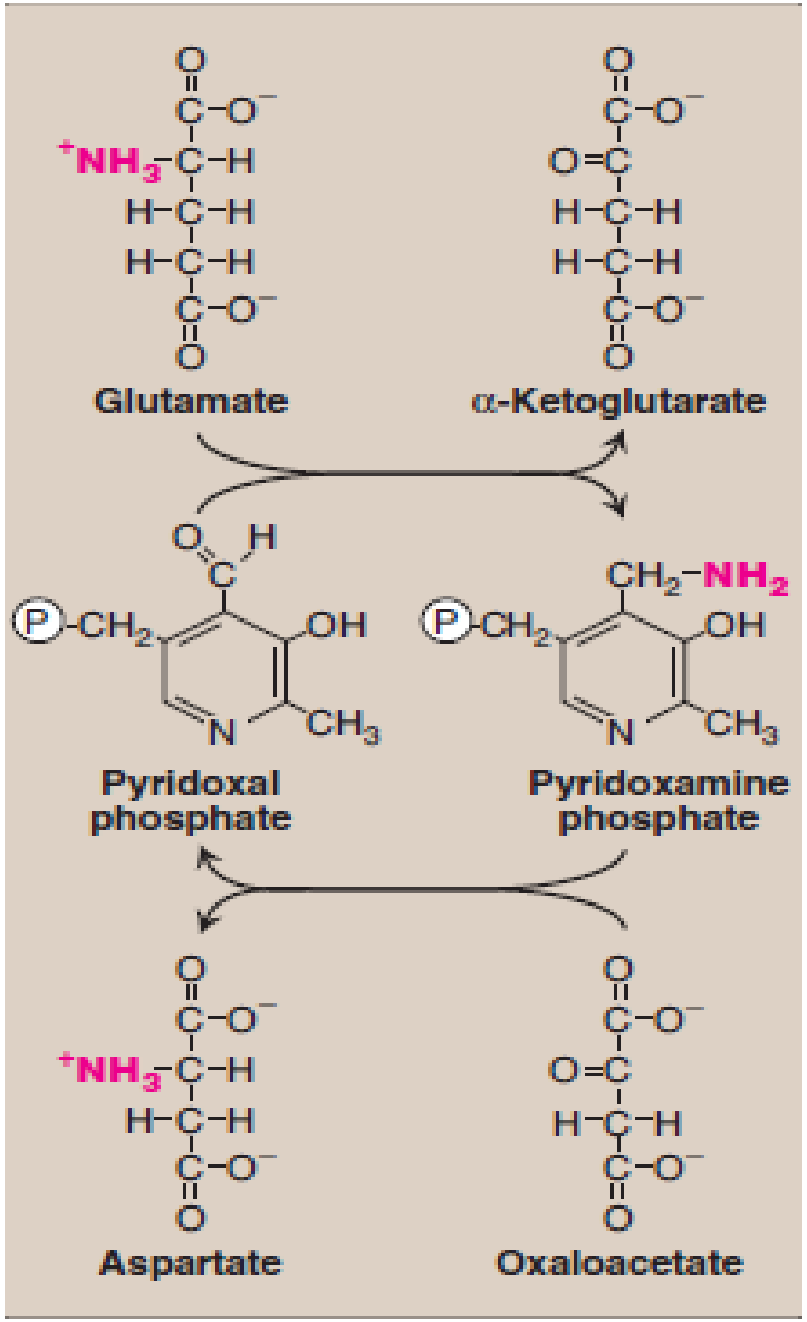



# C. Non oxidative deamination

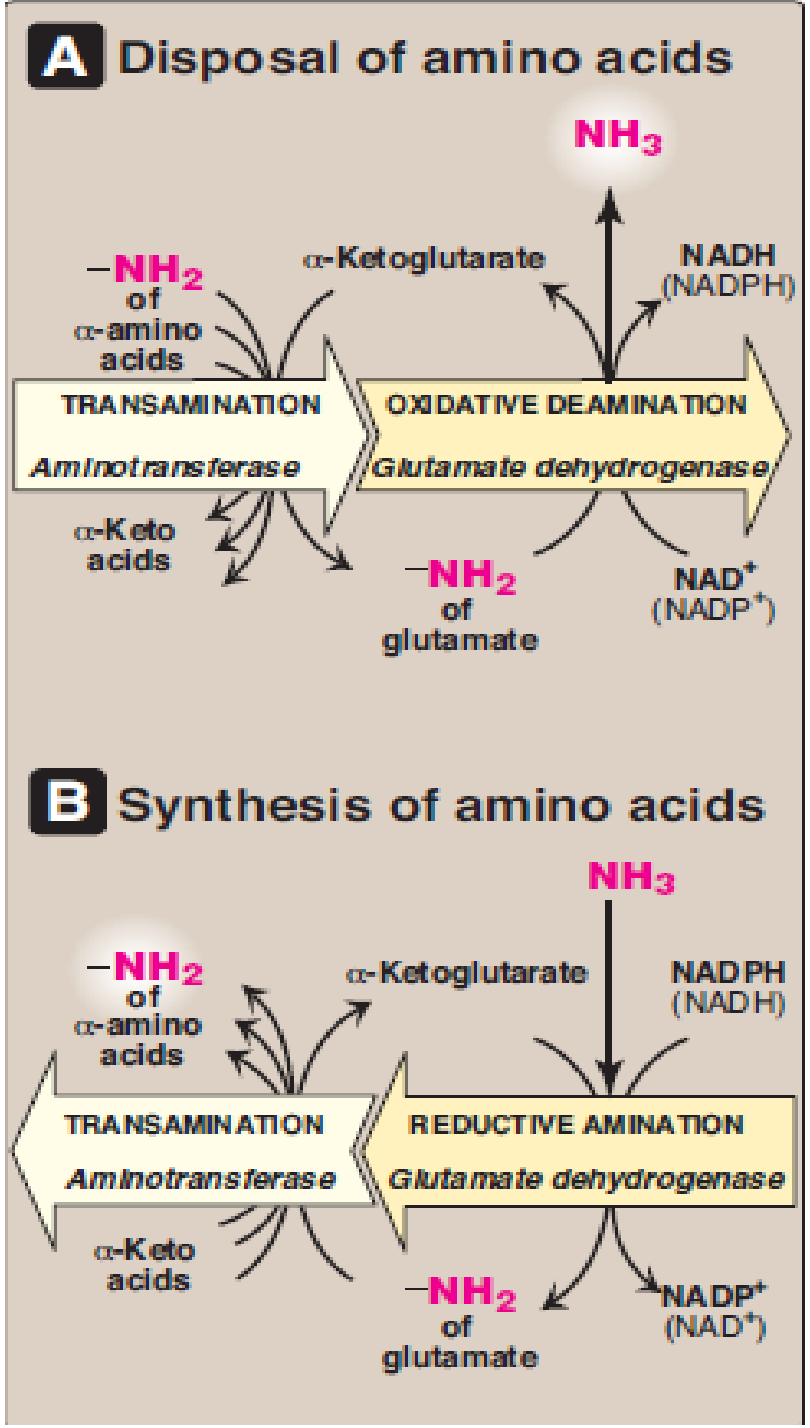
- Some of the amino acids can be deaminated to liberate NH3 without undergoing oxidation (a) Amino acid dehydrases : Serine, threonine and homoserine are the hydroxy amino acids. They undergo non-oxidative deamination catalysed by PLP-dependent dehydrases (dehydratases).
- PLP = pyridoxal phosphate (type of vitamin $B_6$)

# Just to See !!!

Cyclic interconversion of pyridoxal phosphate and pyridoxamine phosphate during the *aspartate aminotransferase* reaction.
[Note: Ⓟ = phosphate group.]

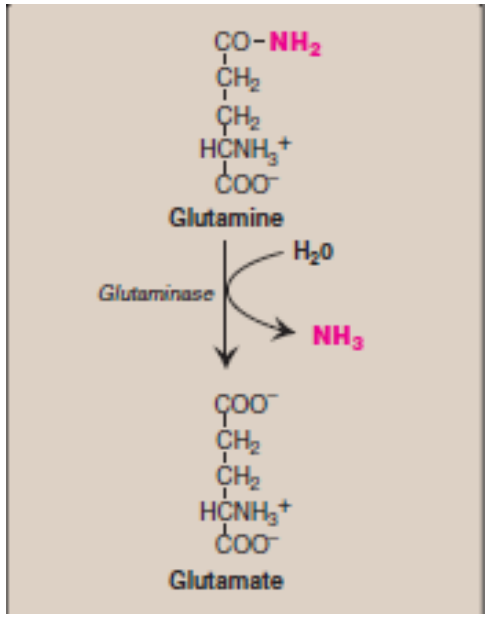


# Combined actions of *aminotransferase* and *glutamate dehydrogenase* reactions

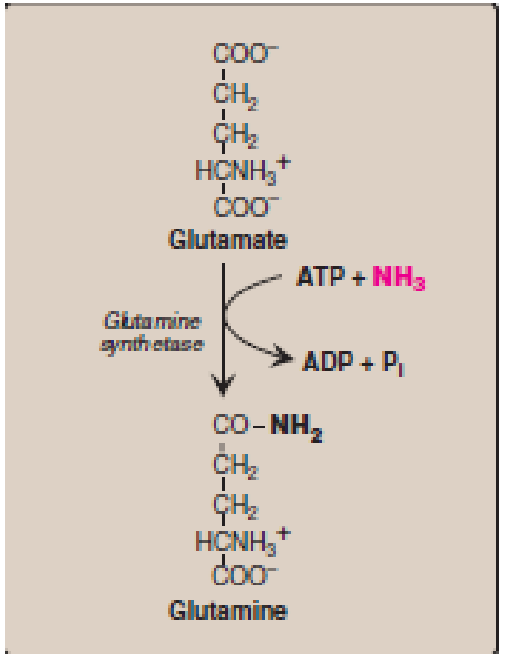


# Transport of ammonia to the liver

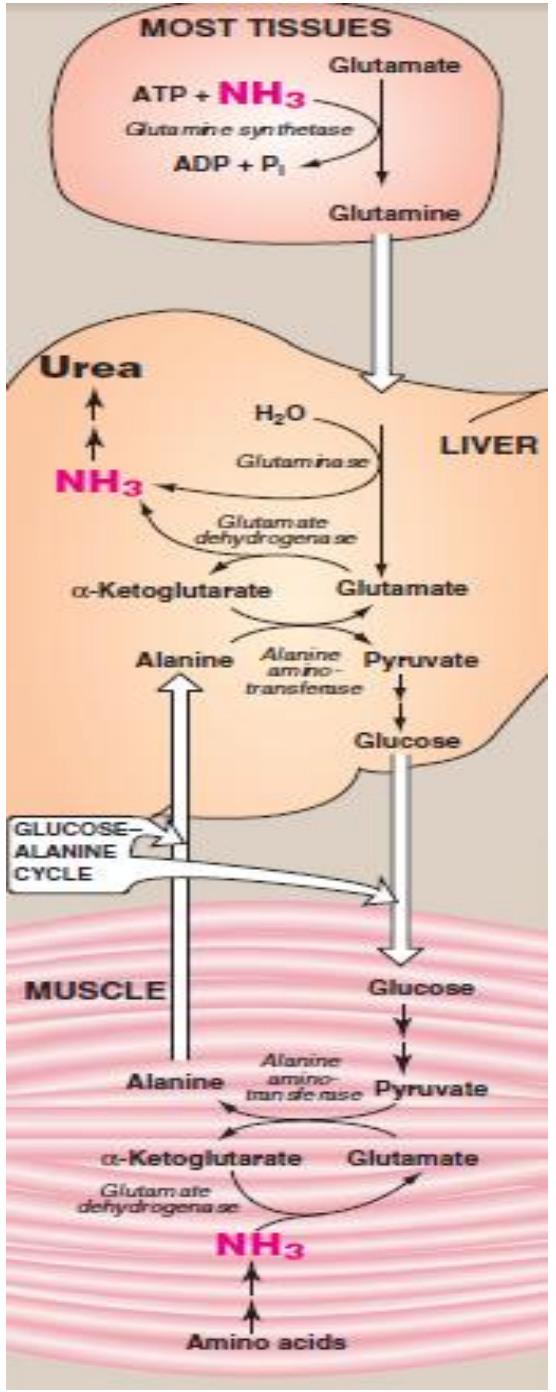
- Two mechanisms are available in humans for the transport of ammonia from the peripheral tissues to the liver for its ultimate conversion to urea. The first, found in most tissues, uses glutamine synthetase to combine ammonia (NH3) with glutamate to form glutamine— a nontoxic transport form of ammonia. The glutamine is transported in the blood to the liver where it is cleaved by glutaminase to produce glutamate and free ammonia (see p. 256). The second transport mechanism, used primarily by muscle, involves transamination of pyruvate (the end product of aerobic glycolysis) to form alanine (see Figure 19.8). Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination. In the liver, the pathway of gluconeogenesis can use the pyruvate to synthesize glucose, which can enter the blood and be used by muscle—a pathway called the glucose-alanine cycle.




Hydrolysis of glutamine to form ammonia.

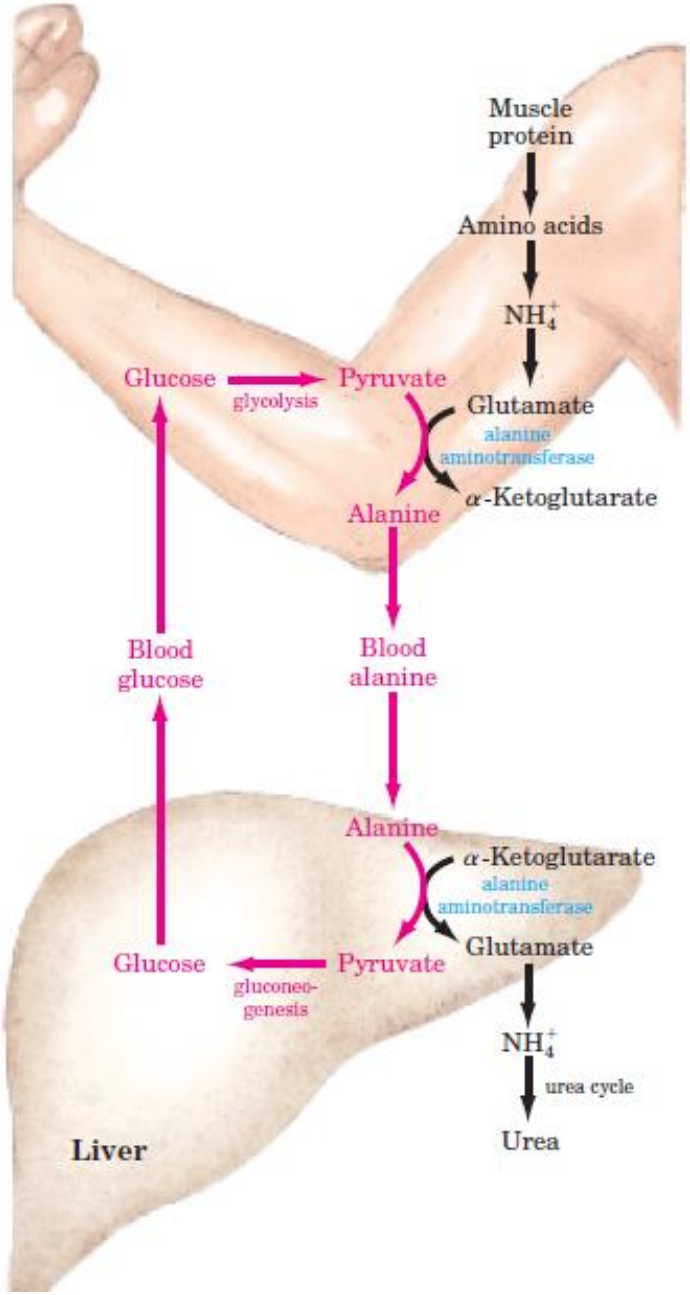



Synthesis of glutamine.



# Glucose-alanine cycle

- Alanine serves as a carrier of ammonia and of the carbon skeleton of pyruvate from skeletal muscle to liver. The ammonia is excreted and the pyruvate is used to produce glucose, which is returned to the muscle.



# Lecture 9
# Urea Cycle and its Fate

Dr. Bilal J M Aldahham

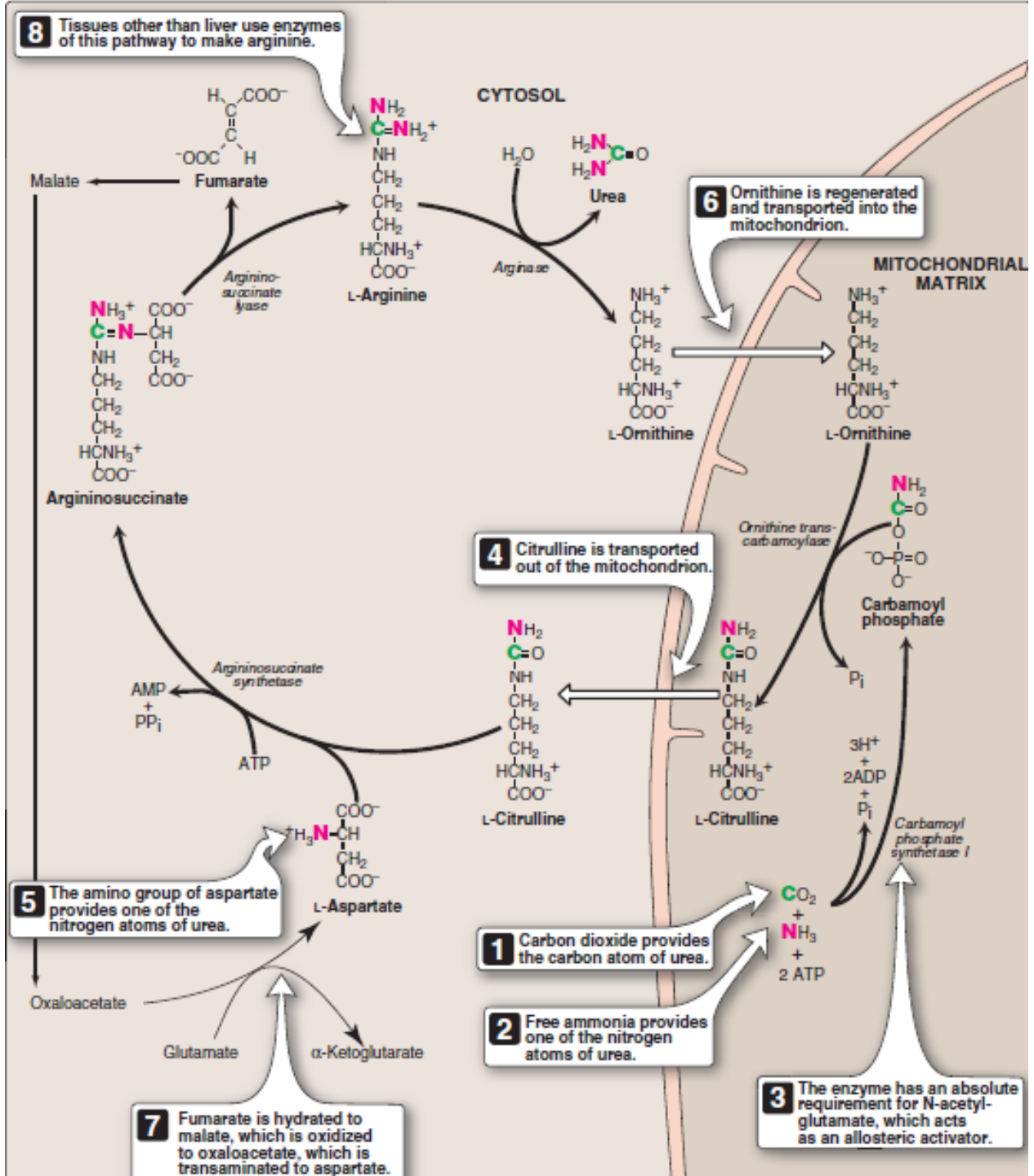
# Urea cycle

- The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol

- 1. Formation of carbamoyl phosphate

(carbamoyl phosphate synthetase I)

- 2. Formation of citrulline (ornithine transcarbamoylase (OTC))
- 3. Synthesis of argininosuccinate: (Argininosuccinate synthetase)
- 4. Cleavage of argininosuccinate (argininosuccinate lyase)
- 5. Cleavage of arginine to ornithine and urea (Arginase)



# 6. Fate of urea

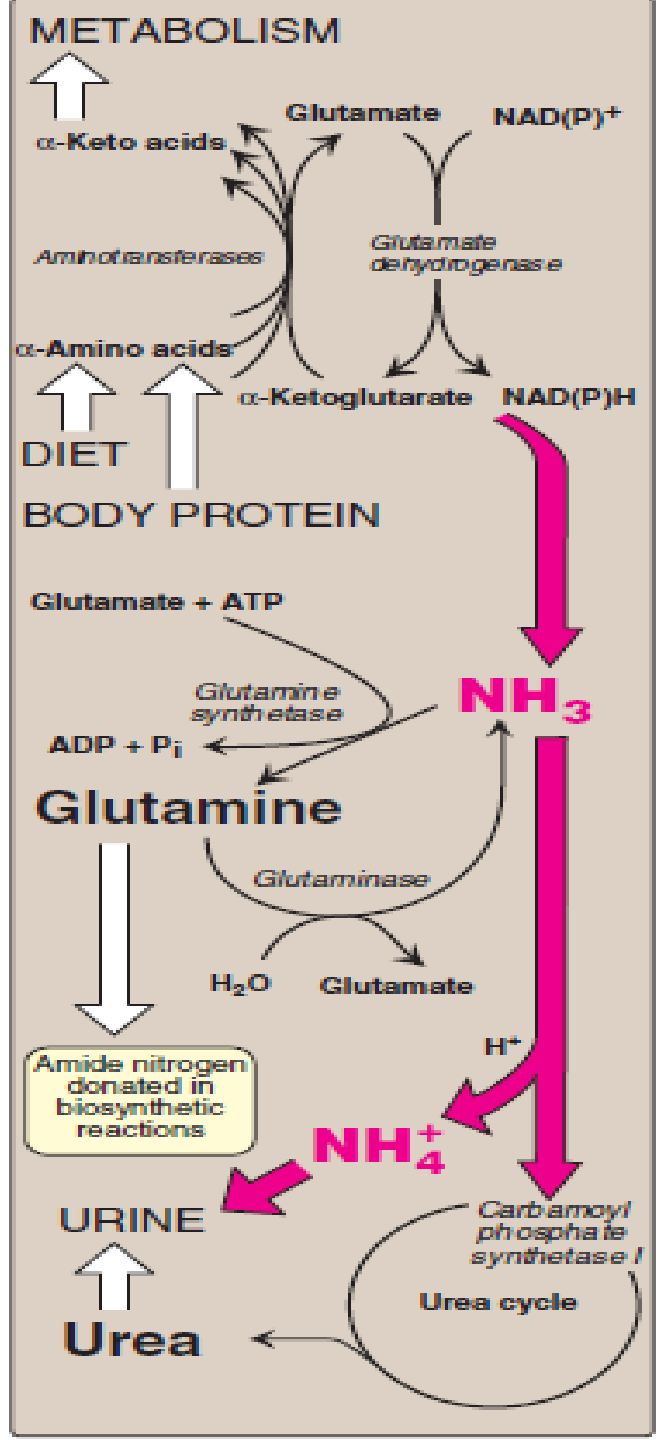
- Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO2 and NH3 by bacterial urease.
- This ammonia is partly lost in the feces, and is partly reabsorbed into the blood.

# Overall stoichiometry of the urea cycle

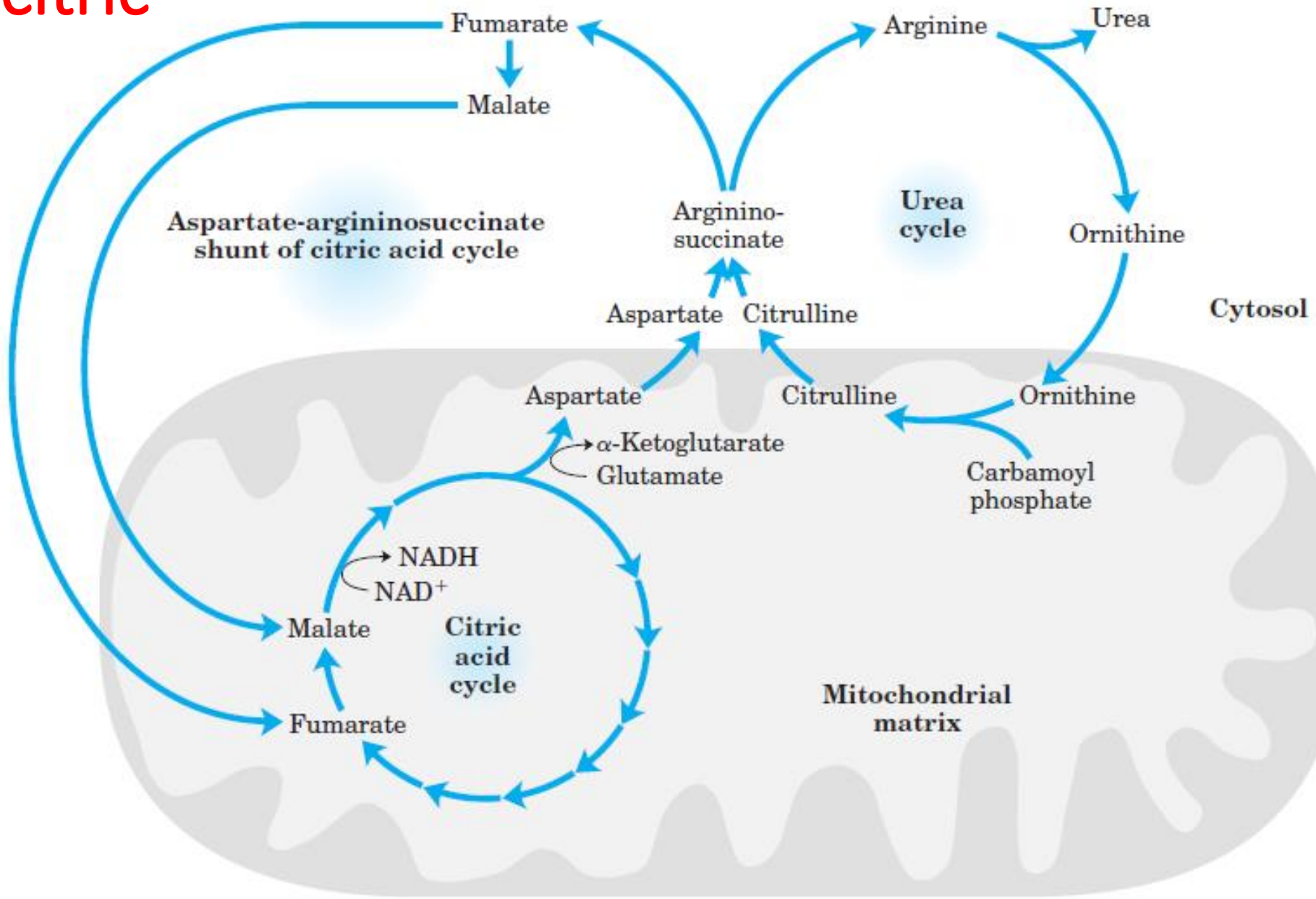
- Aspartate + $NH_3$ + $CO_2$ + 3 ATP + $H_2O$ $\longrightarrow$ urea + fumarate + 2 ADP + AMP + 2 Pi + PPi

# Metabolism of ammonia

- Urea content in the urine is reported as urinary urea nitrogen or UUN. Urea in blood is reported as BUN (blood urea nitrogen).The enzymes *glutamate dehydrogenase*, *glutamine synthetase*, and *carbamoyl phosphate synthetase I* fix ammonia ($NH_3$) into organic molecules.

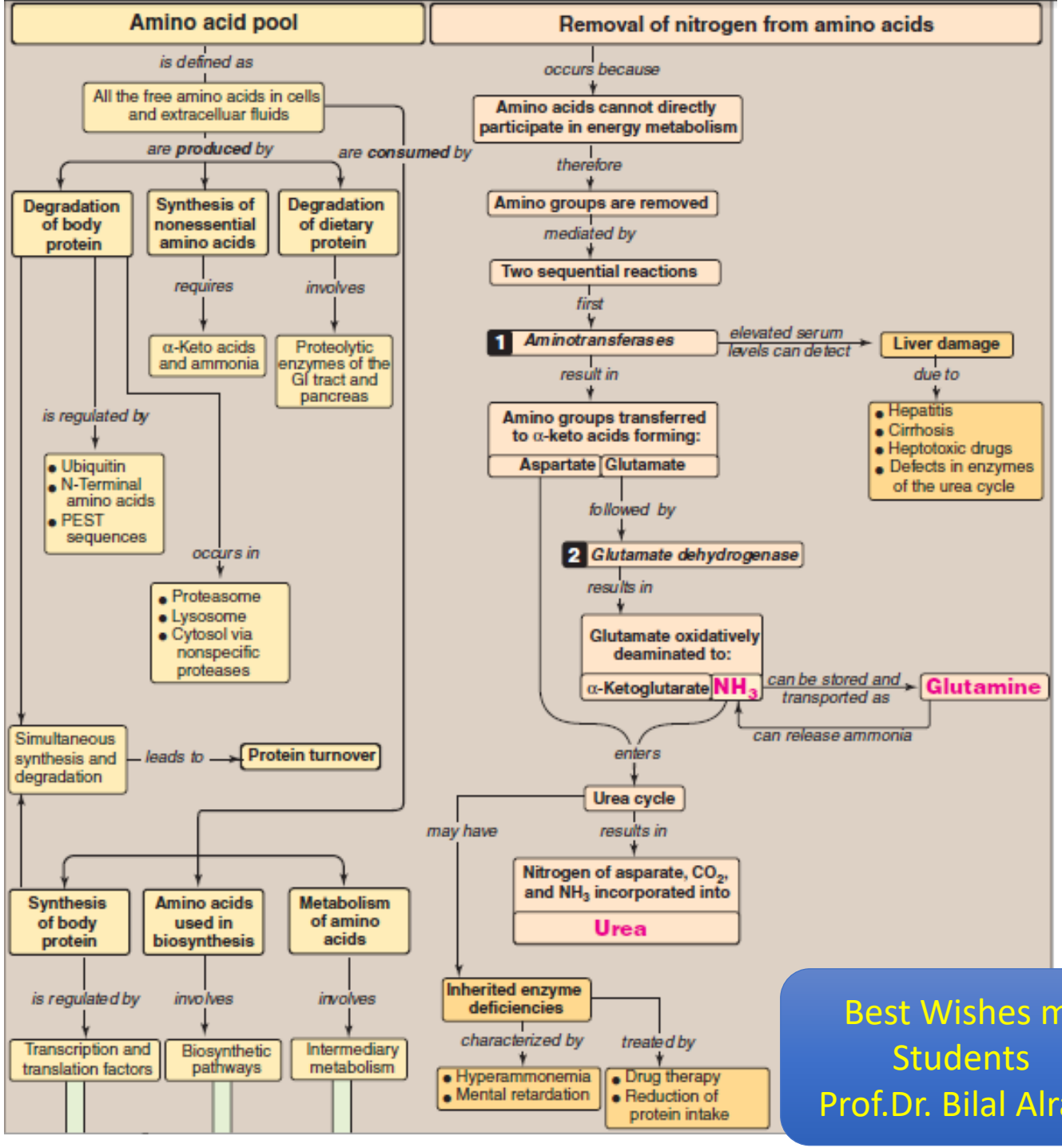


# Links between the urea cycle and citric acid cycle



# SUMMARY

Nitrogen enters the body in a variety of compounds present in food, the most important being amino acids contained in dietary protein. Nitrogen leaves the body as urea, ammonia, and other products derived from amino acid metabolism (Figure 19.21). Free amino acids in the body are produced by hydrolysis of dietary protein by proteases in the stomach and intestine, degradation of tissue proteins, and de novo synthesis. This amino acid pool is consumed in the synthesis of body protein, metabolized for energy, or its members serve as precursors for other nitrogen-containing compounds. Note that body protein is simultaneously degraded and resynthesized— a process known as protein turnover. For many proteins, regulation of synthesis determines the concentration of the protein in the cell, whereas the amounts of other proteins are controlled by selective degradation. The ATP-dependent ubiquitin/proteasome and ATP-independent lysosomal acid hydrolases are the two major enzyme systems that are responsible for degrading damaged or unneeded proteins. Nitrogen cannot be stored, and amino acids in excess of the biosynthetic needs of the cell are immediately degraded. The first phase of catabolism involves the transfer of the !-amino groups by PLP-dependent transamination, followed by oxidative deamination of glutamate, forming ammonia and the corresponding !-keto acids. A portion of the free ammonia is excreted in the urine, some is used in converting glutamate to glutamine, but most is used in the synthesis of urea, which is quantitatively the most important route for disposing of nitrogen from the body. The two major causes of hyperammonemia (with its CNS effects) are liver disease and inherited deficiencies of enzymes (such as ornithine transcarbamolyase) in the urea cycle.




Best Wishes my Students
Prof.Dr. Bilal Alrawi

# Lecture 10
# Obesity and metabolism

Prof Dr Bilal Al Rawi

# scheme

- I. OVERVIEW
- II. ASSESSMENT OF OBESITY
- A. Body mass index
- B. Anatomic differences in fat deposition
- 1. Subcutaneous and visceral depots
- C. Biochemical differences in regional fat depots
- 1. Endocrine function
- 2. Importance of portal circulation
- D. Size and number of fat cells
- III. BODY WEIGHT REGULATION
- A. Genetic contributions to obesity
- 1. Mutations
- B. Environmental and behavioral contributions
- IV. MOLECULES THAT INFLUENCE OBESITY
- A. Long-term signals
- 1. Leptin
- 2. Insulin
- B. Short-term signals
- V. METABOLIC CHANGES OBSERVED IN OBESITY
- A. Metabolic syndrome
- VI. OBESITY AND HEALTH
- VII. WEIGHT REDUCTION
- A. Physical activity
- B. Caloric restriction
- C. Pharmacologic treatment
- D. Surgical treatment

# I. OVERVIEW

- Obesity is a disorder of body weight regulatory systems characterized

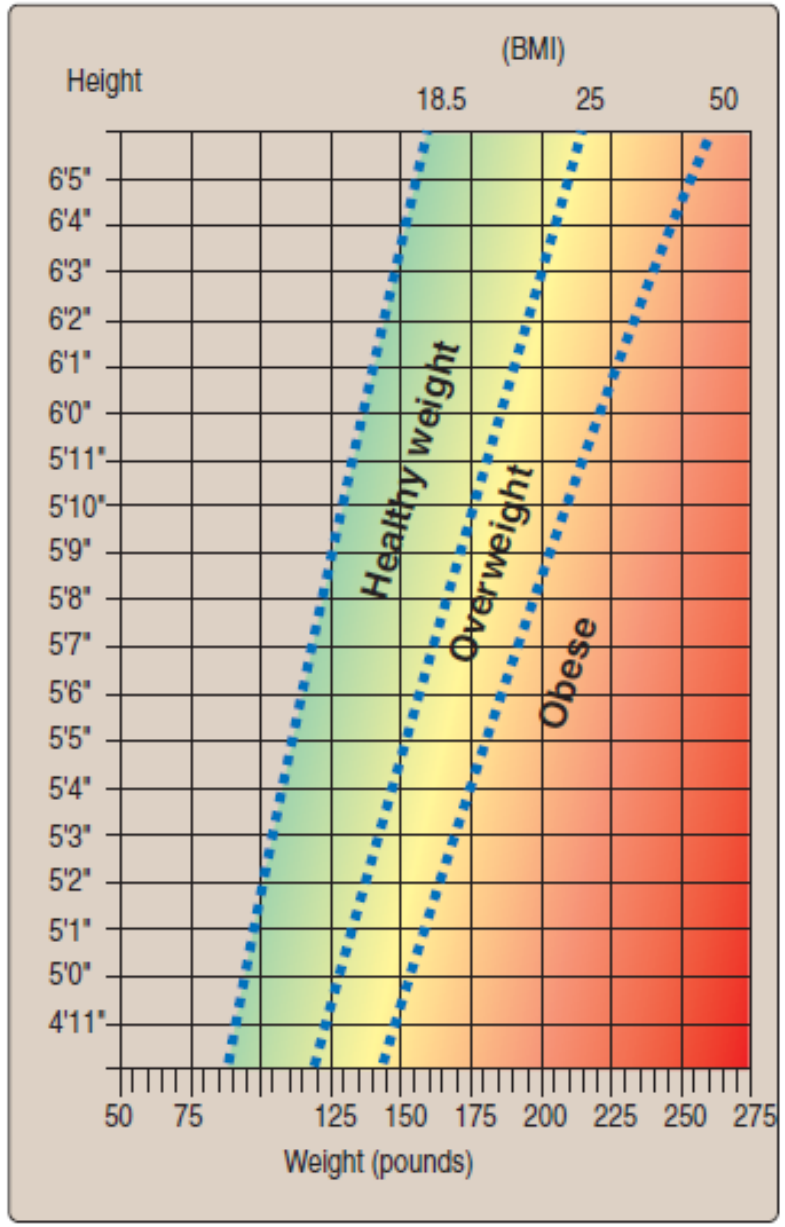
by an accumulation of excess body fat.

- Today, however, the sedentary lifestyle and abundance and wide variety of palatable, inexpensive foods in industrialized societies has undoubtedly contributed to an obesity epidemic.
- As adiposity has increased so has the risk of developing associated diseases, such as arthritis, diabetes, hypertension, cardiovascular disease, and cancer. Particularly alarming is the explosion of obesity in children and adolescents, which has shown a three-fold increase in prevalence over the last two decades.

# II. ASSESSMENT OF OBESITY

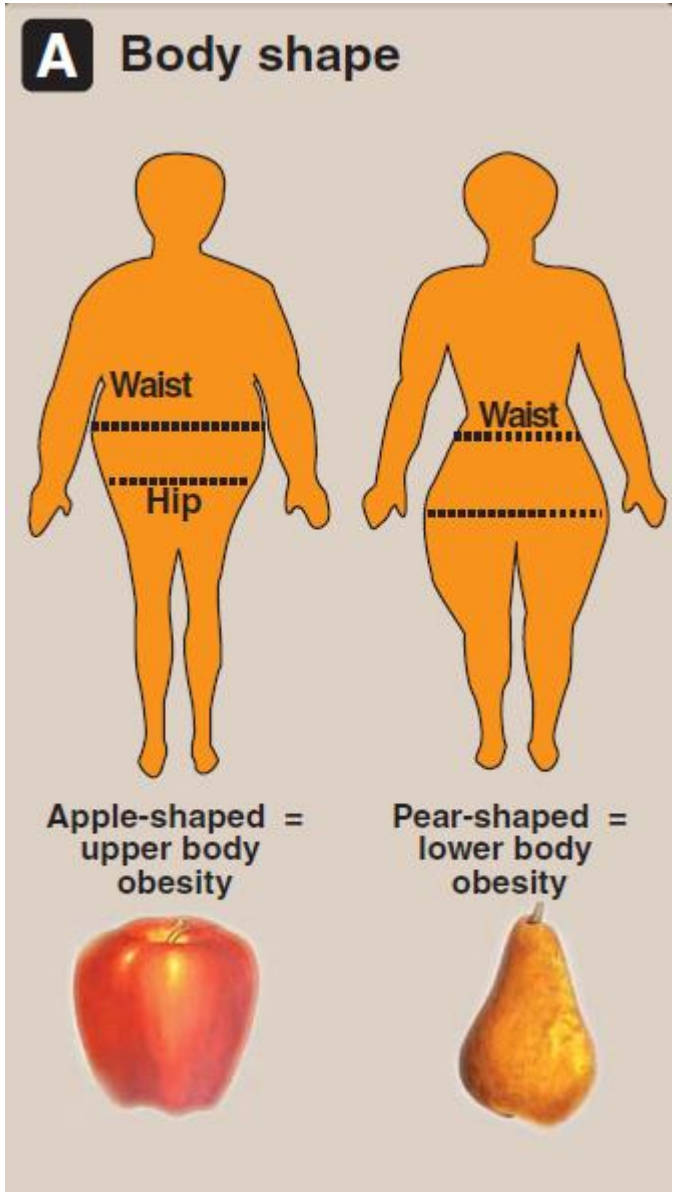
## A. Body mass index

The BMI (weight in kg)/(height in meters)$^2$ provides a measure of relative weight, adjusted for height. This allows comparisons both within and between populations. The healthy range for the BMI is between 18.5 and 24.9. Individuals with a BMI between 25 and 29.9 are considered overweight, those with a BMI equal to or greater than 30 are defined as obese, and a BMI over 40 is considered extremely obese. Anyone more than 100 pounds overweight is considered severely obese (Figure 26.1). These cutoffs are based on the studies examining the relationship of BMI to premature death, and are similar in men and women. Nearly two thirds of American adults are overweight, and more than one third are obese.



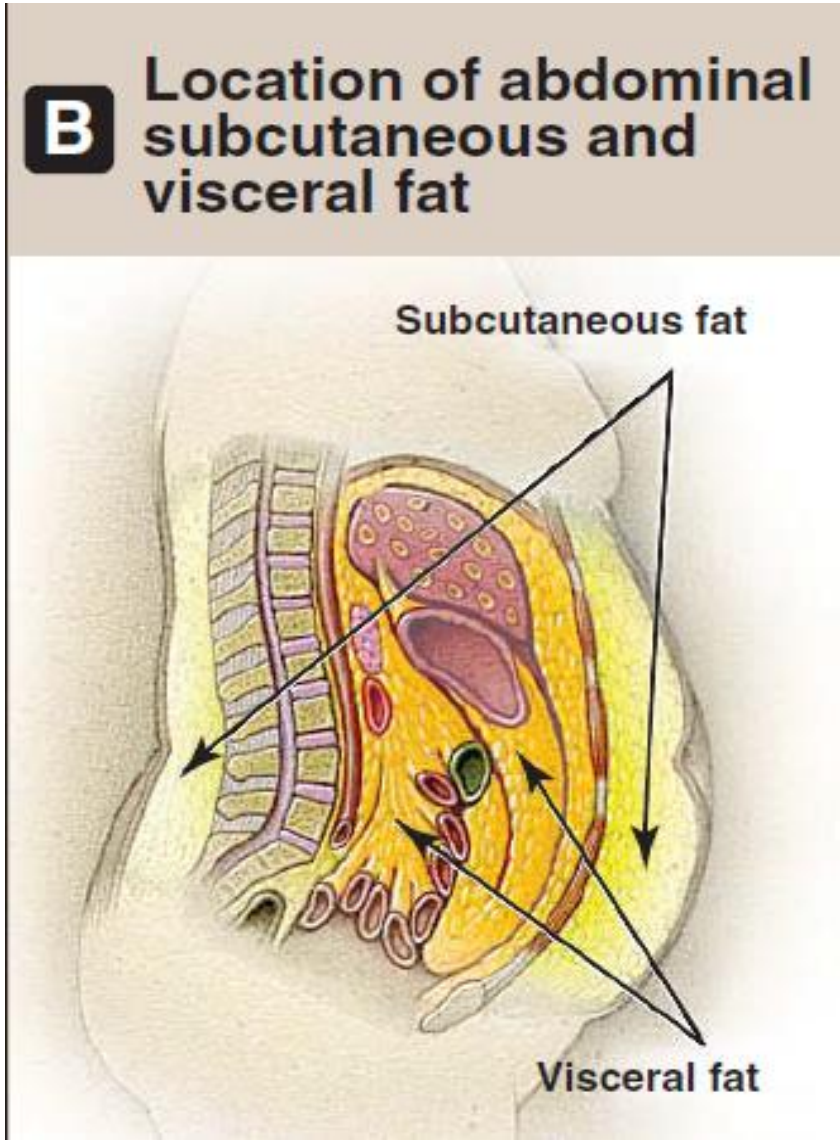
# B. Anatomic differences in fat deposition

The anatomic distribution of body fat has a major influence on associated health risks. A waist to hip ratio of more than 0.8 for women and more than 1.0 for men is defined as android, "apple-shaped," or upper body obesity, and is associated with more fat deposition in the trunk (Figure 26.2A). In contrast, a lower waist to hip ratio reflects a preponderance of fat distributed in the hips and thighs and is called gynoid, "pear-shaped," or lower body obesity. It is defined as a waist to hip ratio of less than 0.8 for women and less than 1.0 for men. The pear shape, more commonly found in women, presents a much lower risk of metabolic disease, and some studies indicate it may actually be protective. Thus, the clinician can use simple indices of body shape to identify those who may be at higher risk for metabolic diseases associated with obesity.



# Subcutaneous and visceral depots

**Subcutaneous and visceral depots:** About 80–90% of the fat stored in the human body is in subcutaneous depots, just under the skin, in the abdominal (upper body) and the gluteal-femoral (lower body) regions. In addition, 10–20% of body fat is stored in so-called visceral depots (omental and mesenteric), which are located within the abdominal cavity in close association with the digestive tract (Figure 26.2B). Excess fat in visceral stores (and also in abdominal subcutaneous fat) increases health risks associated with obesity.

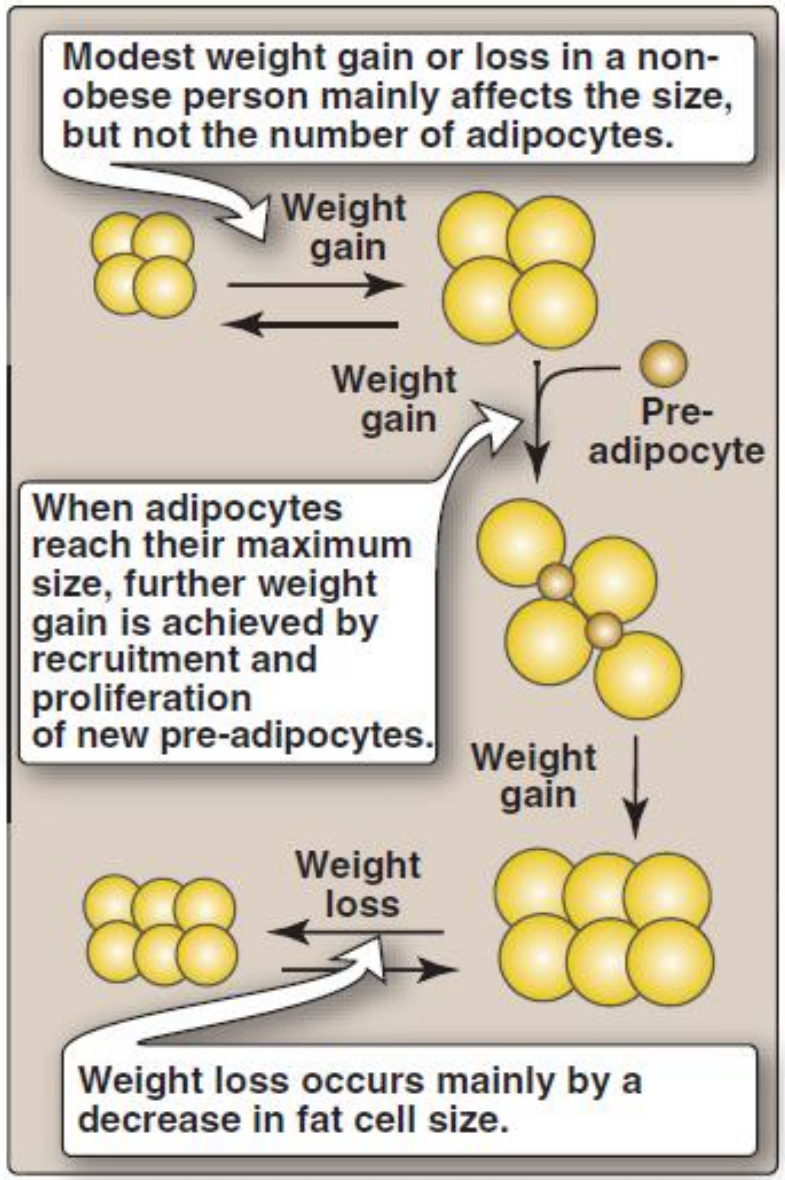


**Endocrine function:** Adipose tissue, once thought to be a passive bystander in metabolism, is now known to play an active role in body weight regulatory systems. For example, the adipocyte is an endocrine cell that secretes a number of hormones, such as leptin, which regulates appetite as well as metabolism (see p. 353). Adiponectin, an adipocyte-derived cytokine, reduces levels of blood free fatty acids and has been associated with improved lipid profiles, better glycemic control, and reduced inflammation in diabetic patients.

**Importance of portal circulation:** One reason that visceral adipose depots may have such a large influence on metabolic dysfunction in obesity is that cytokines secreted by adipose tissue, as well as free fatty acids released from abdominal fat, enter the portal vein and, therefore, have direct access to the liver. Fatty acids and inflammatory cytokines released from visceral adipose tissue are taken up by the liver. They may lead to insulin resistance (see p. 342) and increased synthesis of triacylglycerols, which are released as very-low-density lipoprotein (VLDL) particles and contribute to hypertriglyceridemia (see p. 353). By contrast, free fatty acids from subcutaneous body adipose depots enter the general circulation where they can be oxidized in muscle and, therefore, reach the liver in lower concentration.

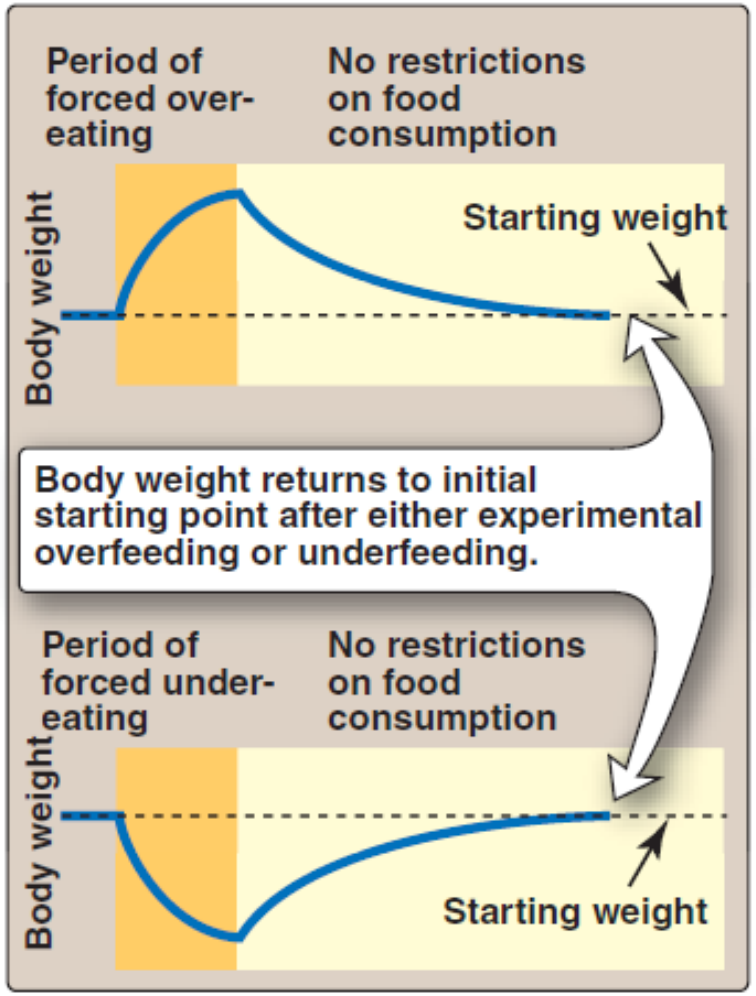
# D. Size and number of fat cells

As triacylglycerols are stored, adipocytes can expand to an average of two to three times their normal volume. (Figure 26.3). However, the ability of a fat cell to expand is limited. With prolonged over-nutrition, preadipocytes within adipose tissue are stimulated to proliferate and differentiate into mature fat cells, increasing the number of adipocytes. Thus, most obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia). Like other tissues, the adipose tissue undergoes continuous remodeling. Contrary to early dogma, we now know that adipocytes can die, but it is uncertain how fast this process occurs; some studies estimate that the average age of an adipocyte is 10 years.



# III. BODY WEIGHT REGULATION

The body weight of most individuals tends to be relatively stable over time. This observation prompted the hypothesis that each individual has a biologically predetermined "set point" for body weight. The body attempts to add to adipose stores when the body weight falls below the set point, and to lose adipose stores when the body weight is higher than the set point. For example, with weight loss, appetite increases and energy expenditure falls, whereas with overfeeding, appetite falls and energy expenditure may slightly increase (Figure 26.4). However, a strict set point model does not explain why some individuals fail to revert to their starting weight after a period of overeating, or the current epidemic of obesity. It appears that factors in the environment (availability of food and exercise) influence a 'settling point' that is defended. Body weight, rather than being irrevocably set, seems to drift around a "settling point," reflecting a balance between environmental factors that influence food intake and energy expenditure, and biologic factors that control body weight.



# A. Genetic contributions to obesity

It is now evident that genetic mechanisms play a major role in determining body weight. The importance of genetics as a determinant of obesity is indicated by the observation that children who are adopted usually show a body weight that correlates with their biologic rather than adoptive parents. Furthermore, identical twins have very similar BMI (Figure 26.5), whether reared together or apart, and their BMI are more similar than those of nonidentical, dizygotic twins.

1. **Mutations:** Rare, single gene mutations can cause human obesity. Mutations in the gene for the adipocyte hormone leptin or its receptor produce hyperphagia (increased appetite for and consumption of food) and massive obesity (Figure 26.6), underscoring the importance of the leptin system in regulation of human body weight (section IV). Most obese humans have elevated leptin levels but appear to be resistant to the appetite-regulating effects of this hormone.

# B. Environmental and behavioral contributions

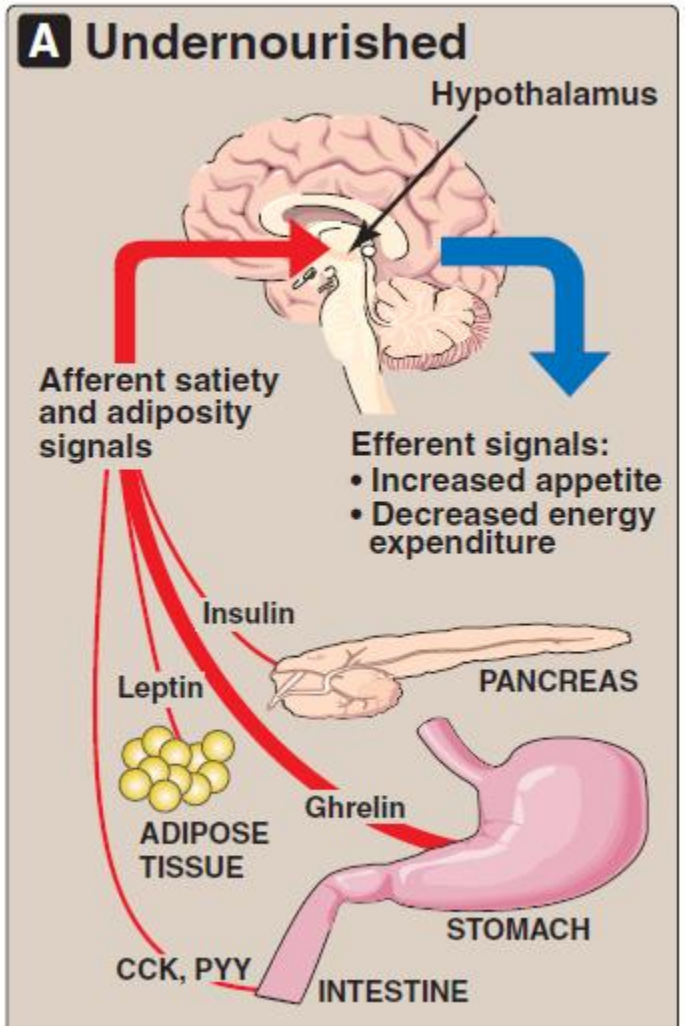
# IV. MOLECULES THAT INFLUENCE OBESITY

**A. Long-term signals.**

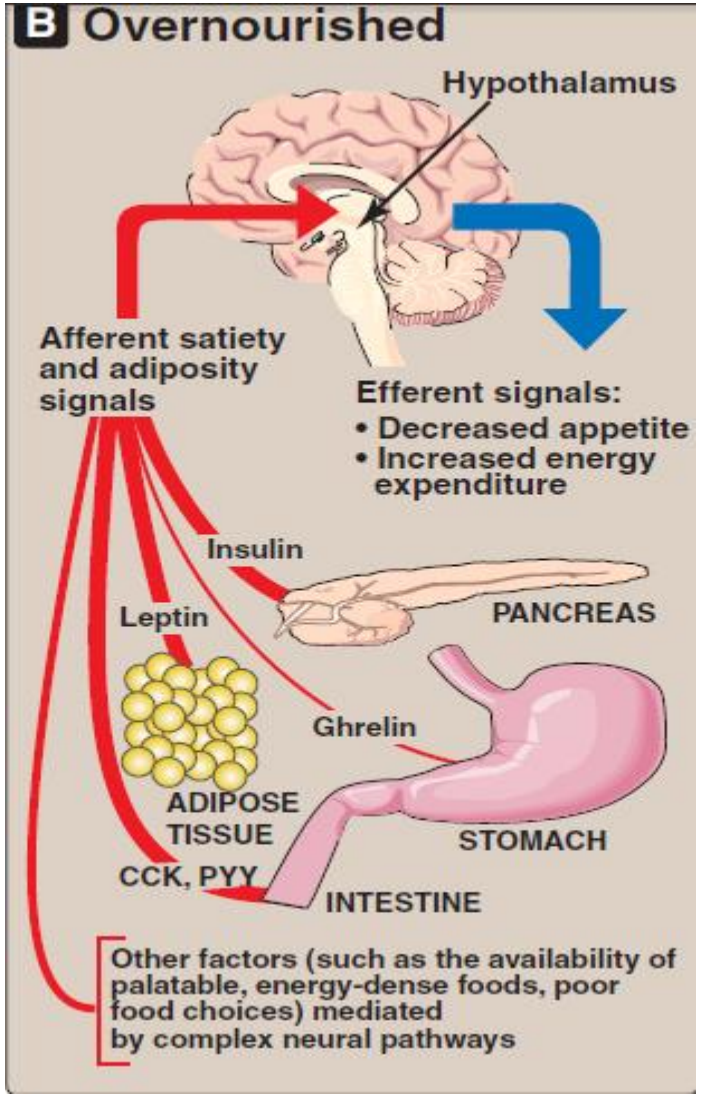
1. **Leptin:** Leptin is an adipocyte hormone that is secreted in proportion to the size of fat stores. When we consume fewer calories than we need, body fat declines and leptin production from the fat cell decreases. The body adapts by minimizing energy utilization (decreasing activity) and increasing appetite, closing the feedback loop that regulates body weight. Unfortunately, in many individuals, the leptin system may be better at preventing weight loss than preventing weight gain. Although a meal or overeating increases leptin and this should, in theory, also dampen appetite and prevent overconsumption of calories, other cues that stimulate appetite can apparently overcome the leptin system in many individuals.

2. **Insulin:** Obese individuals are also hyperinsulinemic. Like leptin, insulin acts on hypothalamic neurons to dampen appetite.

# B. Short-term signals




Some signals that influence appetite and satiety. CCK = cholecystokinin, PYY = peptide YY



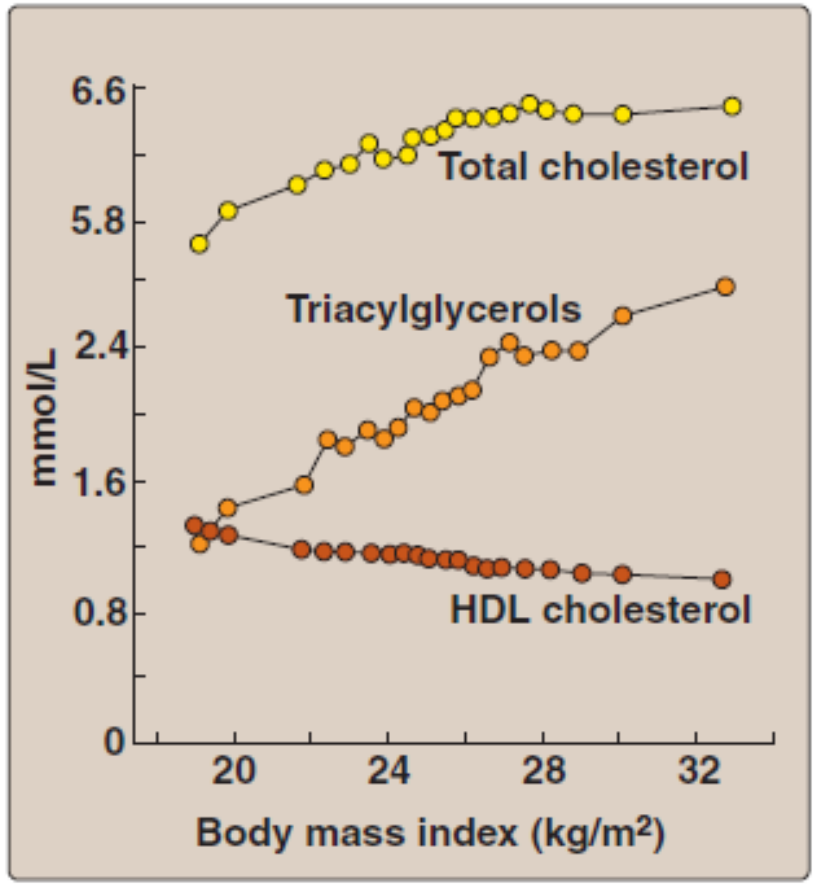
# V. METABOLIC CHANGES OBSERVED IN OBESITY

- The primary metabolic effects of obesity include dyslipidemias, glucose intolerance (hyperglycemia below that classified as diabetes), and insulin resistance, expressed primarily in the liver, muscle, and adipose tissue. These metabolic abnormalities reflect molecular signals originating from the increased mass of adipocytes.

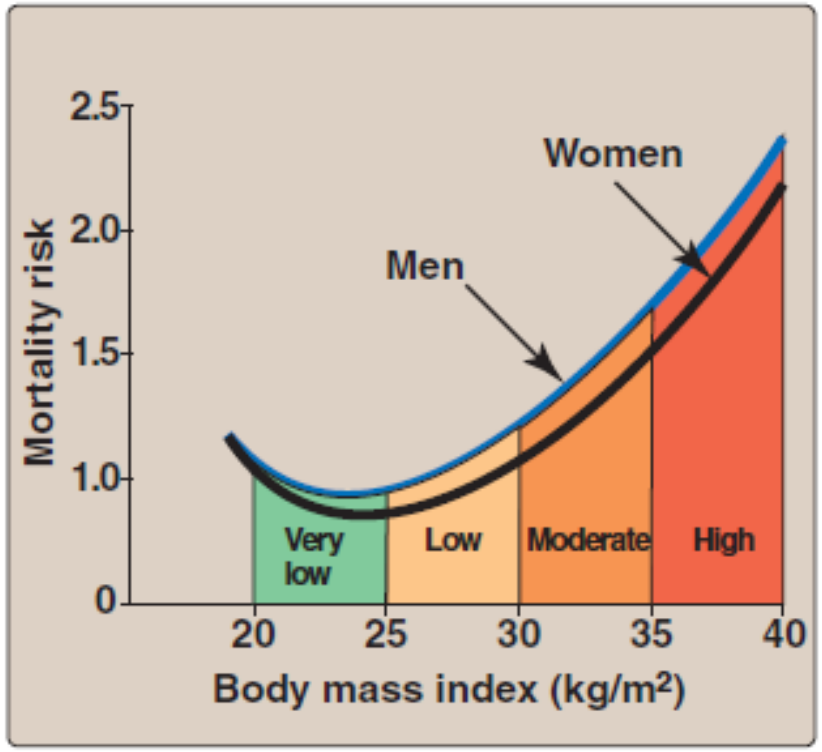
# A. Metabolic syndrome

Abdominal obesity is associated with a cluster of metabolic abnormalities that is referred to as the metabolic syndrome and includes glucose intolerance, insulin resistance, hyperinsulinemia, dyslipidemia (low high-density lipoprotein (HDL) and elevated triacylglycerols), and hypertension (Figure 26.8). The metabolic syndrome is also associated with a state of chronic systemic inflammation that contributes to the pathogenesis of insulin resistance and atherosclerosis. In obesity, low levels of the adipocyte hormone adiponectin

that normally dampens inflammation and sensitizes tissues, especially the liver, to insulin, may contribute to the metabolic syndrome and therefore the risk of type 2 diabetes and heart disease.



# VI. OBESITY AND HEALTH



# VII. WEIGHT REDUCTION

- A. Physical activity
- An increase in physical activity can create an energy deficit. Although adding exercise to a hypocaloric regimen may not produce a greater weight loss initially, exercise is a key component of programs directed at maintaining a weight loss. In addition, physical activity increases cardiopulmonary fitness and reduces the risk of cardiovascular disease, independent of weight loss. Persons who combine caloric restriction and exercise with behavioral treatment may expect to lose about 5–10% of initial body weight over a period of 4–6 months. Studies show that individuals who maintain their exercise program regain less weight after their initial weight loss.

- **B. Caloric restriction**
- More than 90% of people who attempt to lose weight regain the lost weight when dietary intervention is suspended. Nonetheless, it is important to recognize that, although few individuals will reach their ideal weight with treatment, weight losses of10% of body weight over a 6-month period often reduce blood pressure and lipid levels, and enhance control of type 2 diabetes. The health benefits of relatively small weight losses should, therefore, be emphasized to the patient.

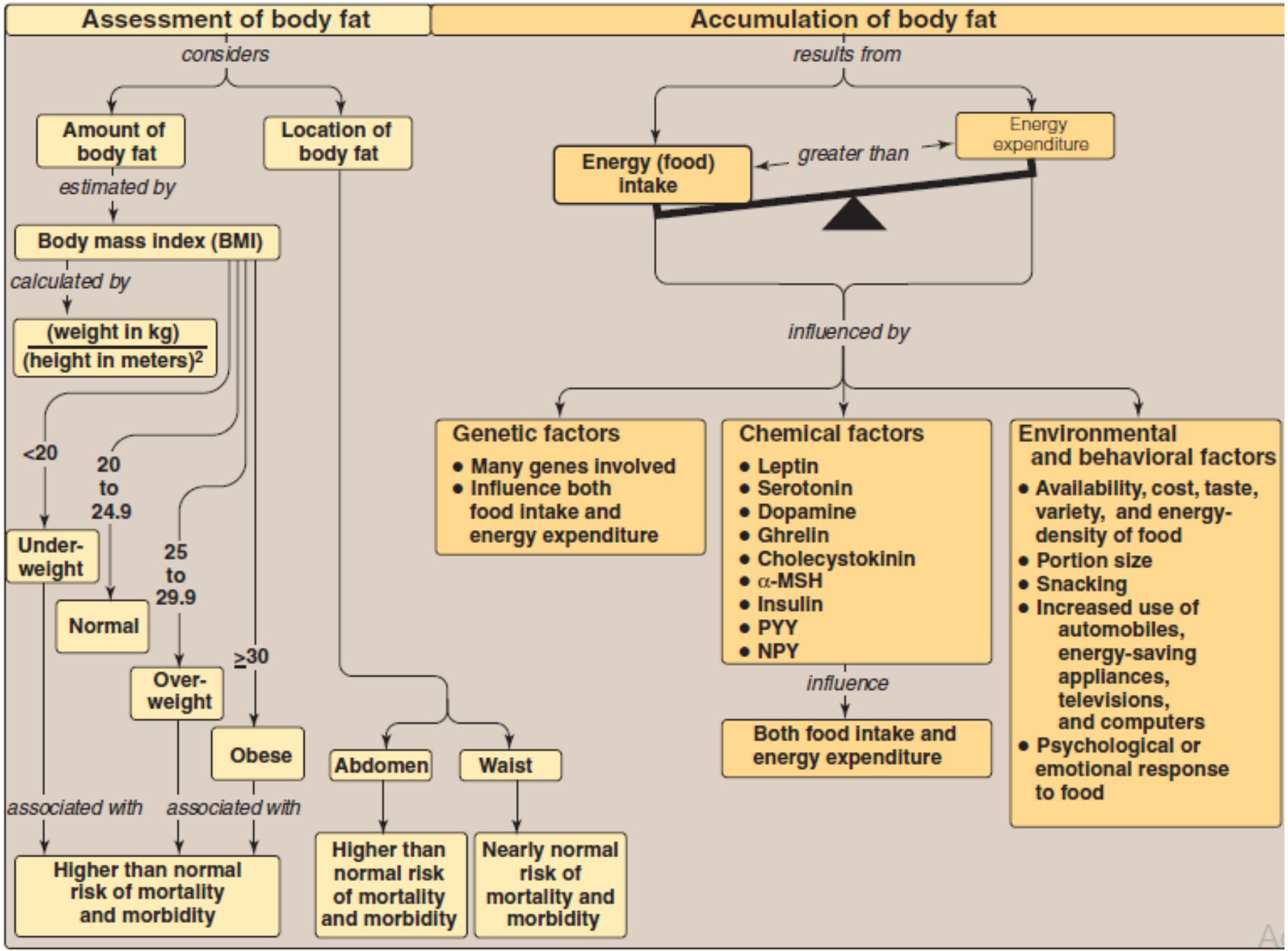
# VII. WEIGHT REDUCTION

## C. Pharmacologlc treatment

Several weight-loss medications are currently approved by the U.S. Food and Drug Administration for use in adults with a BMI of 30 or higher[1]. Their effects on weight reduction tend to be modest, and weight regain upon termination of drug therapy is common.

## D. Surglcal treatment

Gastric bypass and restriction surgeries are effective in causing weight loss in severely obese individuals. Through mechanisms that remain poorly understood, these operations improve poor blood sugar control in diabetic individuals.


Assessment of body fat
considers
Amount of body fat
Location of body fat
estimated by
Body mass index (BMI)
calculated by
(weight in kg) / (height in meters)²
<20
20 to 24.9
25 to 29.9
≥30
Under-weight
Normal
Over-weight
Obese
associated with
associated with
Higher than normal risk of mortality and morbidity
Abdomen
Waist
Higher than normal risk of mortality and morbidity
Nearly normal risk of mortality and morbidity
Accumulation of body fat
results from
Energy (food) intake
greater than
Energy expenditure
influenced by
Genetic factors
• Many genes involved
• Influence both food intake and energy expenditure
Chemical factors
• Leptin
• Serotonin
• Dopamine
• Ghrelin
• Cholecystokinin
• α-MSH
• Insulin
• PYY
• NPY
influence
Both food intake and energy expenditure
Environmental and behavioral factors
• Availability, cost, taste, variety, and energy-density of food
• Portion size
• Snacking
• Increased use of automobiles, energy-saving appliances, televisions, and computers
• Psychological or emotional response to food

# Symmary

**Obesity**—the accumulation of excess body fat—results when energy intake exceeds energy expenditure. Obesity is increasing in industrialized countries because of a reduction in daily energy expenditure, and an increase in energy intake resulting from the increasing availability of palatable, inexpensive foods. The **body mass index (BMI)** is easy to determine and highly correlated to body fat. Nearly two thirds of American adults are **overweight** (BMI $\geq$ 25 kg/m$^2$) and more than 30% are **obese** (BMI > 30 kg/m$^2$). The anatomic distribution of body fat has a major influence on associated health risks. Excess fat located in the **central abdominal** area is associated with greater risk for hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease. A person's weight is determined by genetic and environmental factors. **Appetite** is influenced by **afferent**, or incoming, **signals**—neural signals, circulating hormones, and metabolites—that are integrated by the **hypothalamus.** These diverse signals prompt release of hypothalamic peptides and activate outgoing, efferent neural signals. **Obesity** is correlated with an **increased risk of death**, and is a risk factor for a number of chronic conditions. **Weight reduction** is achieved best with negative energy balance, that is, by **decreasing caloric intake**. Virtually all diets that limit particular groups of foods or macronutrients lead to short-term weight loss. Long-term maintenance of weight loss is difficult to achieve. Modest reduction in food intake occurs with **pharmacologic treatment. Surgical procedures** designed to limit food intake are an option for the severely obese patient who has not responded to other treatments.

# Basal metabolic rate (BMR)

* Energy required by an awake individual during physical emotional and digestive rest
* Minimum amount of energy required for functioning of vital organs like heart, circulation, brain function, respiration etc

# Factors affecting BMR

1. BMR is more in children ( active growth ,5yrs)
2. Males have higher BMR
3. BMR increases in cold climates
4. Increased during exercise
5. Fever
6. Thyroid hormones : Increased in Hyperthyroidism
7. Decreased in starvation

Normal value : 24 kcal/kg bodywt/ day

# Equation of BMR caculation

The Harris–Benedict equations revised by Mifflin and St Jeor in 1990

| | |
|---|---|
| Men | BMR = (10 × weight in kg) + (6.25 × height in cm) - (5 × age in years) + 5 |
| Women | BMR = (10 × weight in kg) + (6.25 × height in cm) - (5 × age in years) - 161 |