Lecture Series 9

Cellular Pathways That Harvest Chemical Energy

Reading Assignments

- Review Chapter 3
  Energy, Catalysis, & Biosynthesis
- Read Chapter 13
  How Cells obtain Energy from Food
- Read Chapter 14
  Energy Generation in Mitochondria & Chloroplasts

A. Energy and Energy Conversions

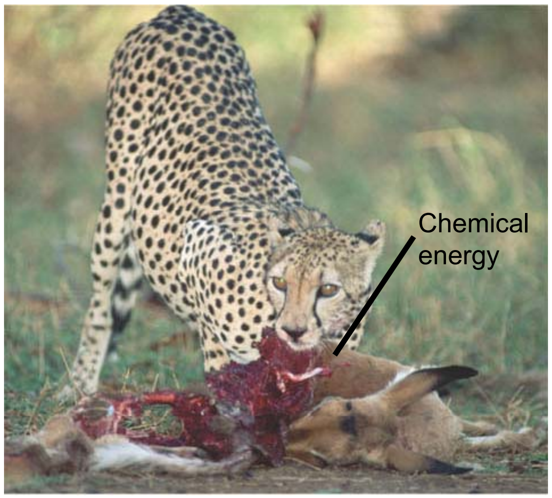
- Energy is the capacity to do work (cause change).
- Potential energy is the energy of state or position; it includes energy stored in chemical bonds. Examples are chemical (candy bar or gasoline) or elevated mass.
- Kinetic energy is the energy of motion. Examples are heat, light and electricity.
- Potential energy can be converted to kinetic energy and vice versa.

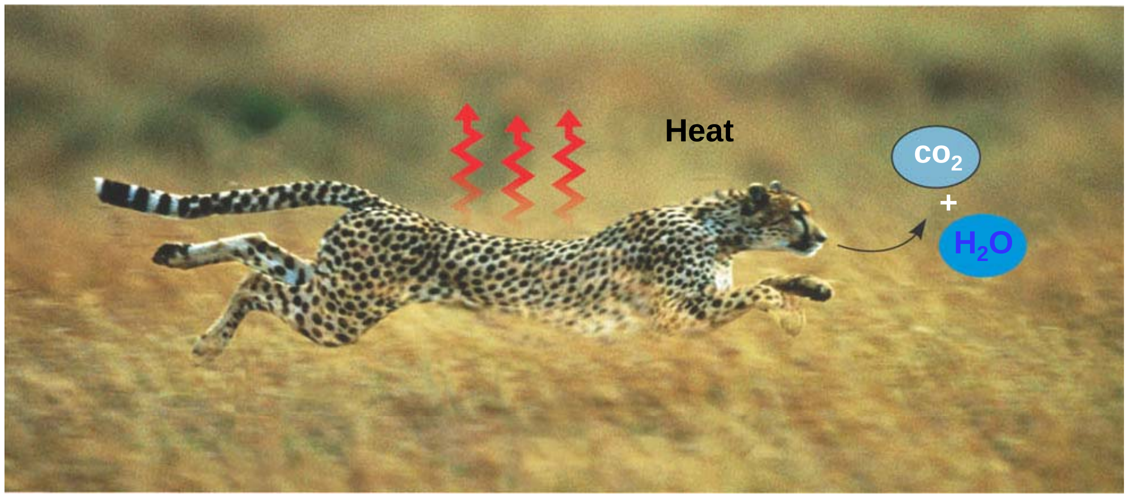
A. Energy and Energy Conversions

- The first law of thermodynamics tells us energy cannot be created or destroyed. [Except when mass is converted to energy, as in the sun where hydrogen is converted to helium with some mass converted to energy.]

- The second tells us that, in a closed system, the quantity of energy available to do work decreases and unusable energy increases. **Entropic doom** = the disorder or entropy of the universe is increasing.

The two laws of thermodynamics



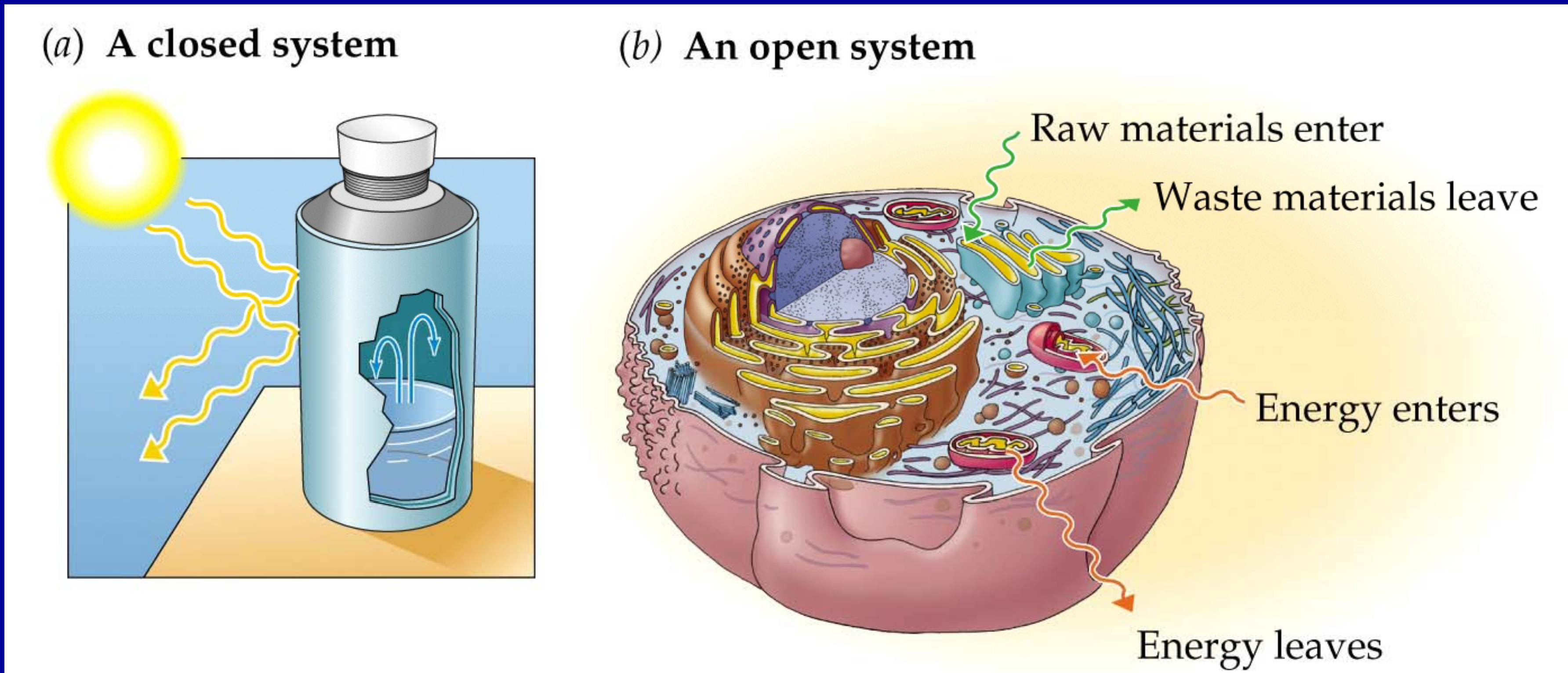


(a) First law of thermodynamics: Energy can be transferred or transformed but neither created nor destroyed. For example, the chemical (potential) energy in food will be converted to the kinetic energy of the cheetah's movement in (b).

(b) Second law of thermodynamics: Every energy transfer or transformation increases the disorder (entropy) of the universe. For example, disorder is added to the cheetah's surroundings in the form of heat and the small molecules that are the by-products of metabolism.

A. Energy and Energy Conversions

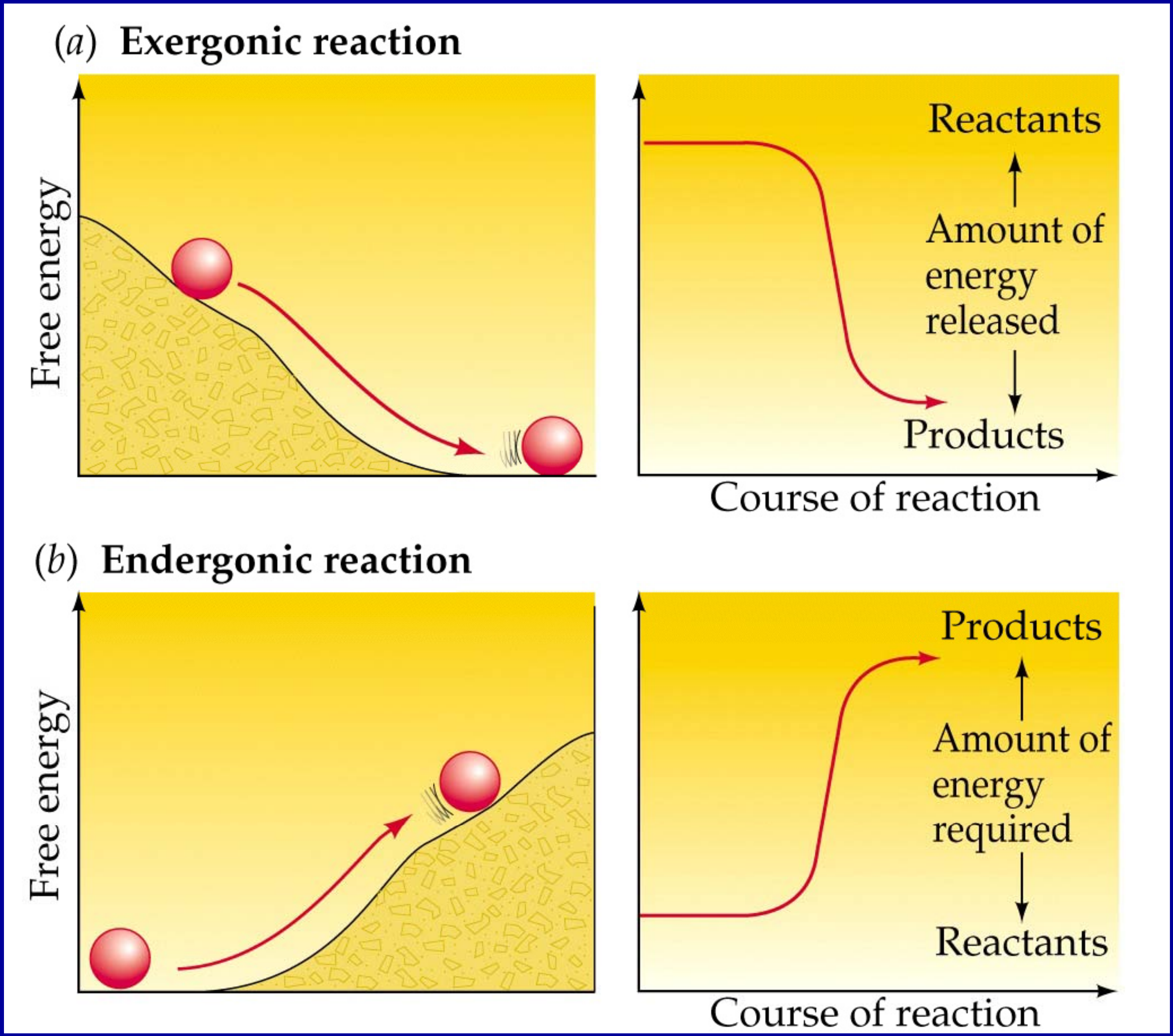
- Living things obey the laws of thermodynamics.
- Cells & Organisms are open systems.


(a) A closed system
(b) An open system
Raw materials enter
Waste materials leave
Energy enters
Energy leaves

A. Energy and Energy Conversions

- Changes in free energy, total energy (enthalpy), temperature, and entropy are related by the equation $\Delta G = \Delta H - T\Delta S$.

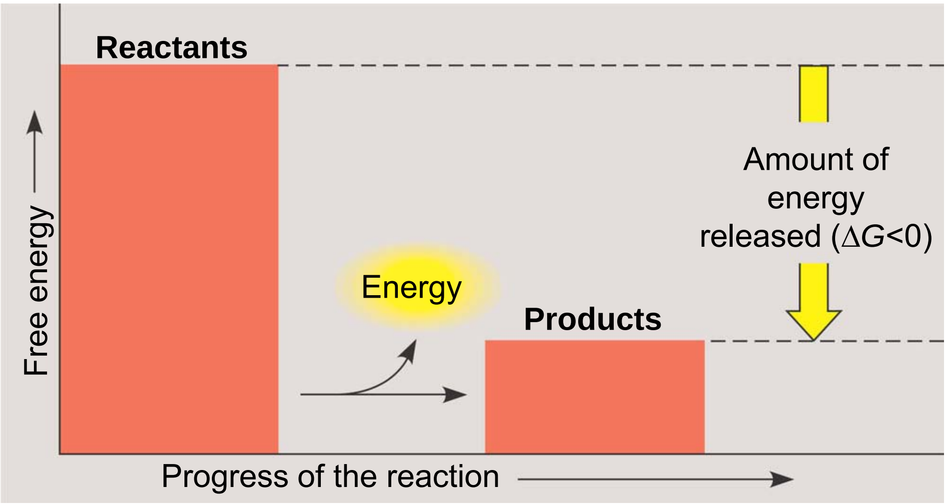
- Spontaneous, exergonic reactions release free energy and have a negative ΔG. Non-spontaneous, endergonic reactions take up free energy, have a positive ΔG, and proceed only if free energy is provided.


(a) Exergonic reaction
Free energy
Reactants
Amount of energy released
Products
Course of reaction
(b) Endergonic reaction
Free energy
Products
Amount of energy required
Reactants
Course of reaction

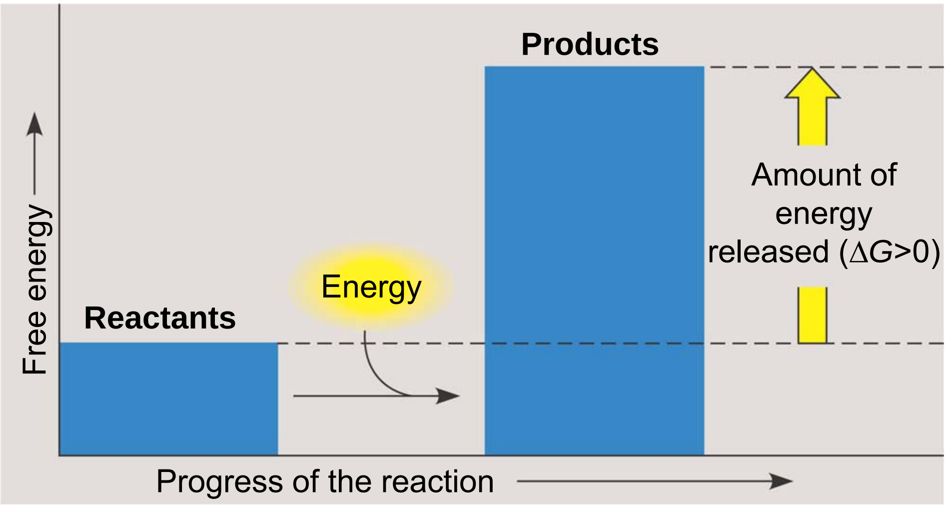
A. Energy and Energy Conversions

- The change in free energy of a reaction determines its point of chemical equilibrium, at which forward and reverse reactions proceed at the same rate.
- For spontaneous, exergonic reactions, the equilibrium point lies toward completion.

Free energy changes (ΔG) in exergonic and endergonic reactions

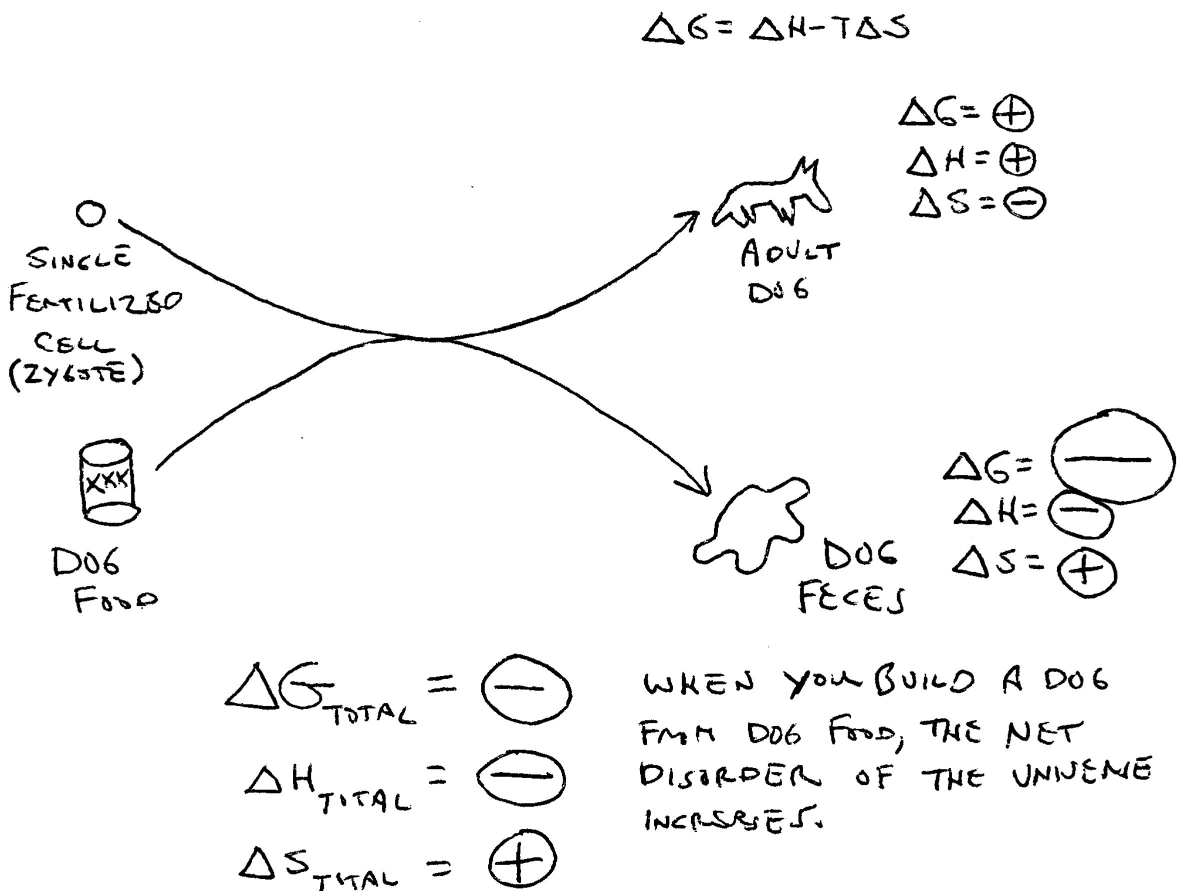


(a) Exergonic reaction: energy released



(b) Endergonic reaction: energy required

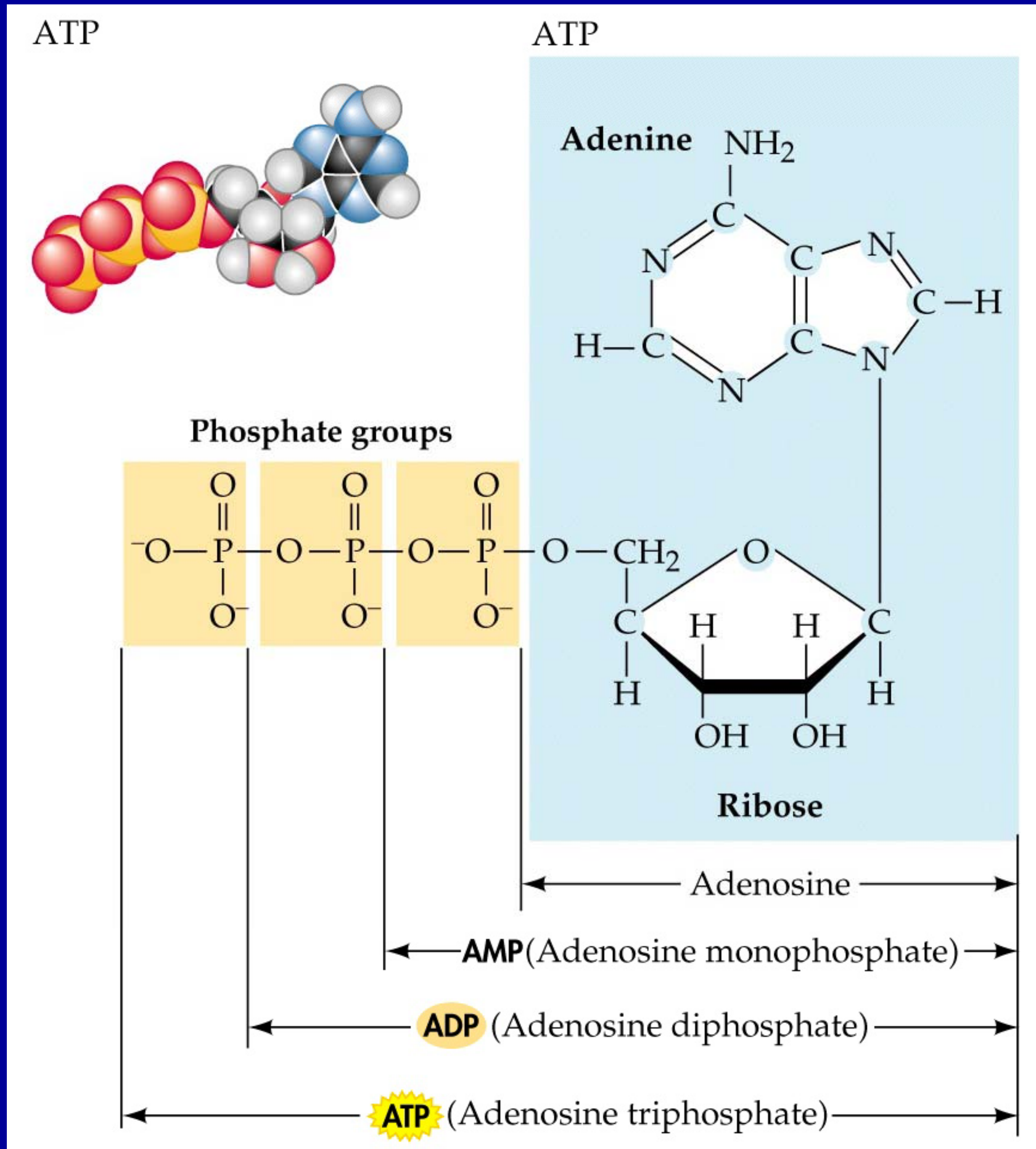
Ordered (living) systems can be built as long as the net disorder of the universe is increased in the process of building that order. Thus living systems adhere to the second law of thermodynamics. If living systems did not adhere, then it wouldn't be a "law". Laws are observations or rules that have been found over hundreds of years of experimentation not to be violated.



Courtesy D. Williams

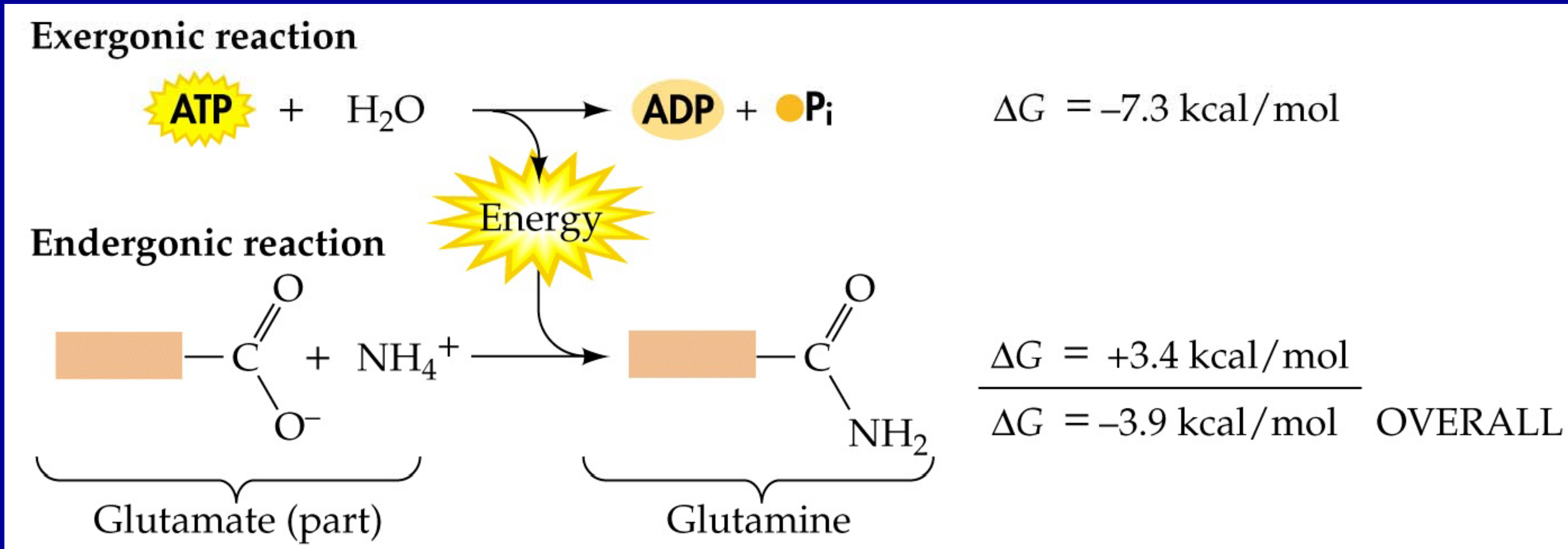
B. ATP: Transferring Energy in Cells

- ATP serves as an energy currency in cells.
- Hydrolysis of ATP releases a relatively large amount of free energy.


ATP
ATP
Adenine
NH_2
Phosphate groups
Ribose
Adenosine
AMP (Adenosine monophosphate)
ADP (Adenosine diphosphate)
ATP (Adenosine triphosphate)

B. ATP: Transferring Energy in Cells

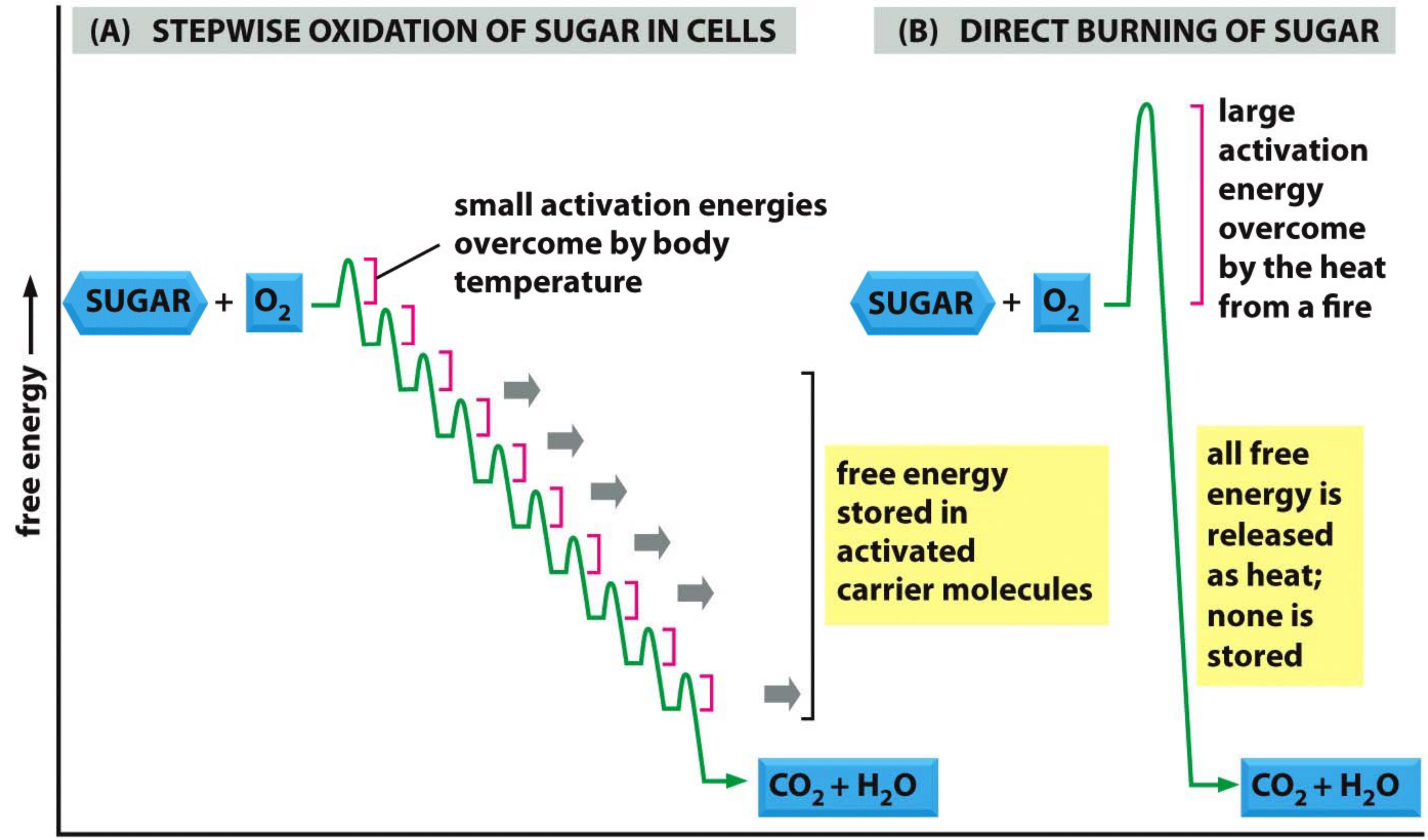
- The ATP cycle couples exergonic and endergonic reactions, transferring free energy from the exergonic to the endergonic reaction.



The way energy is supplied for the formation of glutamine is the following: Glutamate is converted to a phosphate derivative, which makes the molecule electrophilic. Ammonia, because it is nucleophilic, can now attack the phosphate derivative, forming glutamine (GLN).

Cellular Pathways In General

- Metabolic pathways occur in small steps, each catalyzed by a specific enzyme.
- Metabolic pathways are often compartmentalized and are highly regulated.



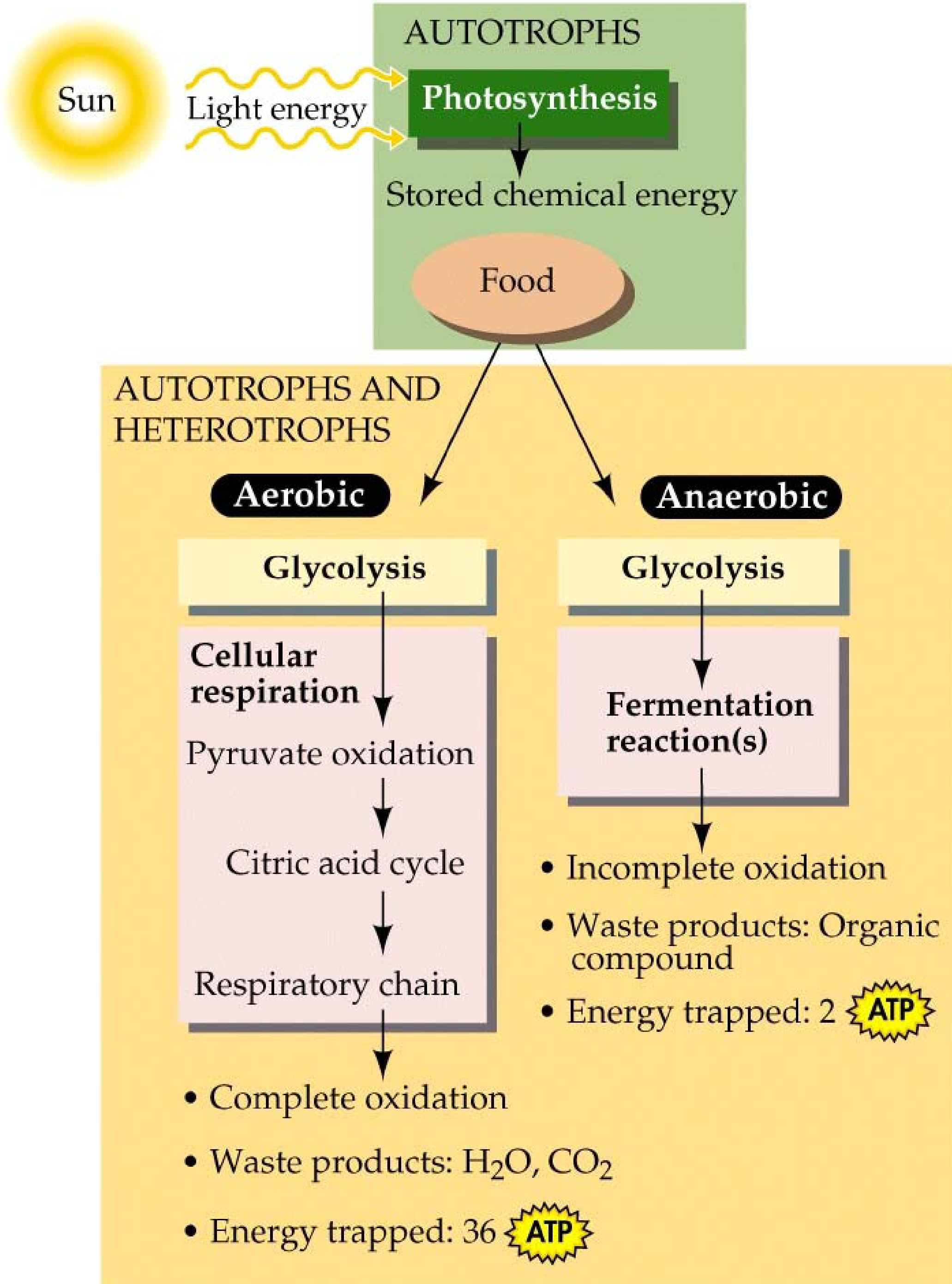
(A) STEPWISE OXIDATION OF SUGAR IN CELLS
(B) DIRECT BURNING OF SUGAR
free energy
SUGAR
+
O2
small activation energies overcome by body temperature
free energy stored in activated carrier molecules
CO2 + H2O
large activation energy overcome by the heat from a fire
all free energy is released as heat; none is stored

C. Obtaining Energy and Electrons from Glucose

- When glucose burns, energy is released as heat and light:

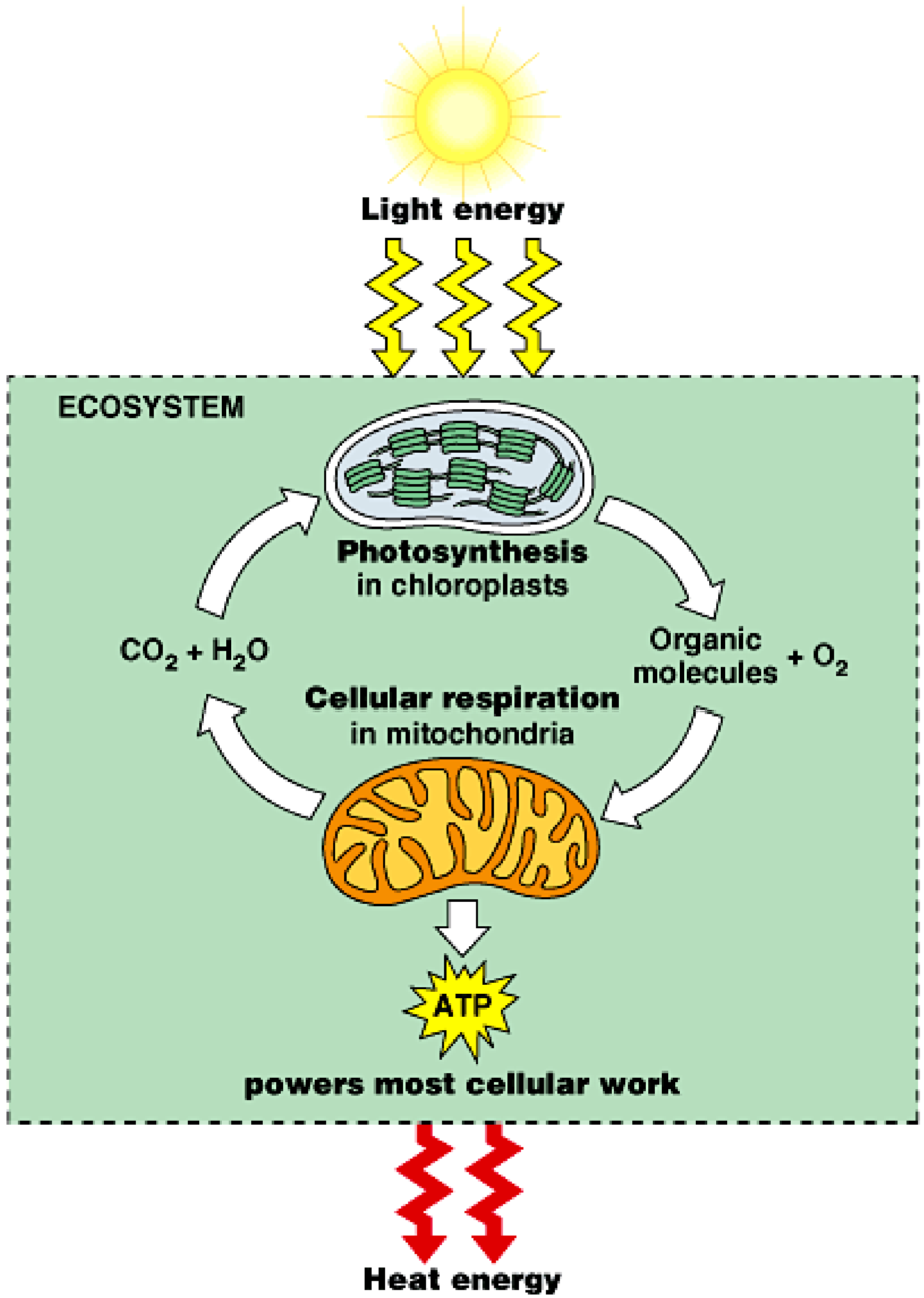
  $C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_20 + energy$

- The same equation applies to the metabolism of glucose by cells, but the reaction is accomplished in many separate steps so that the energy can be captured as ATP with minimal loss as heat.

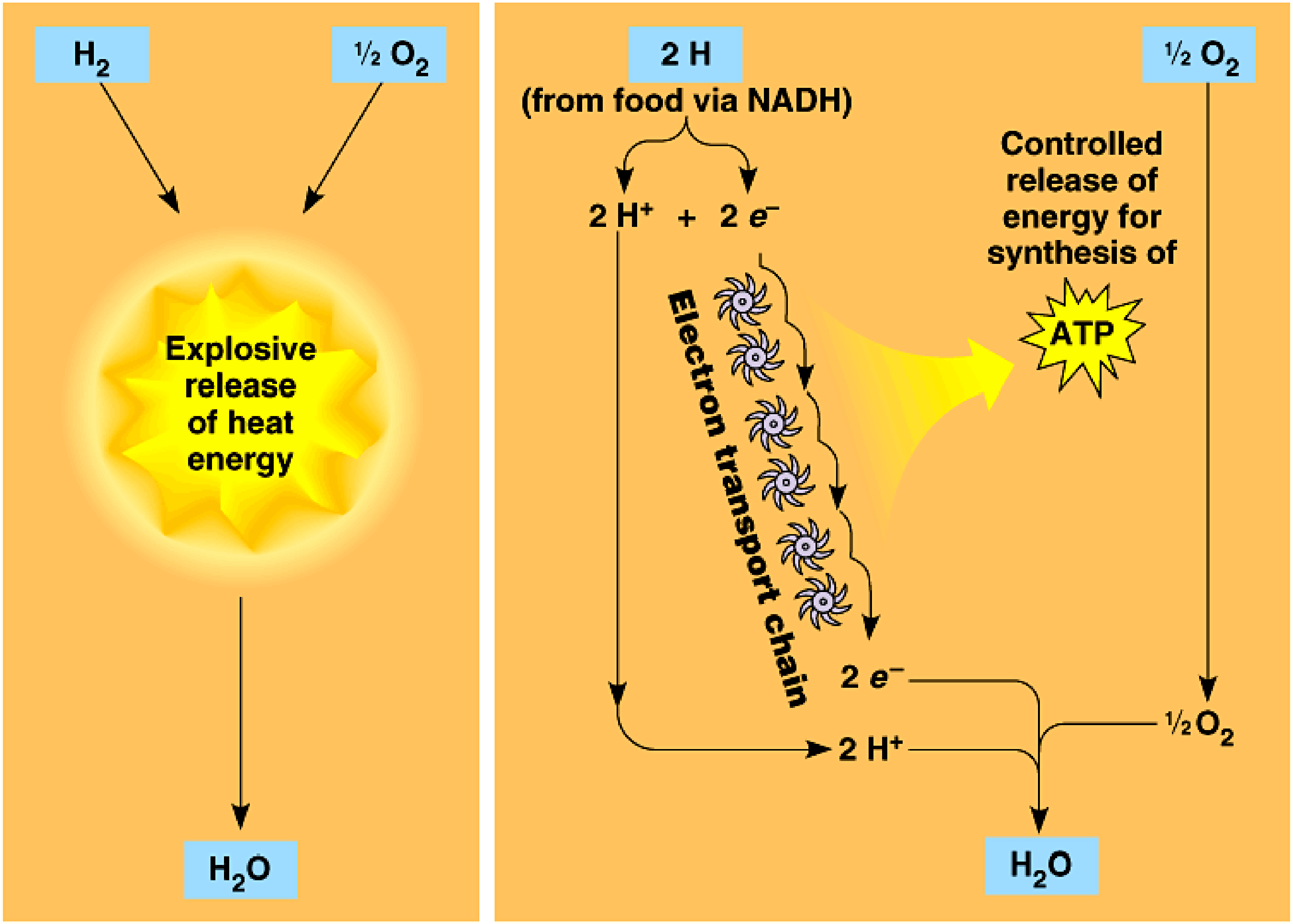


AUTOTROPHS
Sun
Light energy
Photosynthesis
Stored chemical energy
Food
AUTOTROPHS AND HETEROTROPHS
Aerobic
Anaerobic
Glycolysis
Cellular respiration
Pyruvate oxidation
Citric acid cycle
Respiratory chain
• Complete oxidation
• Waste products: H_2O, CO_2
• Energy trapped: 36 ATP
Glycolysis
Fermentation reaction(s)
• Incomplete oxidation
• Waste products: Organic compound
• Energy trapped: 2 ATP

Energy flow and chemical recycling in ecosystems



An introduction to electron transport chains

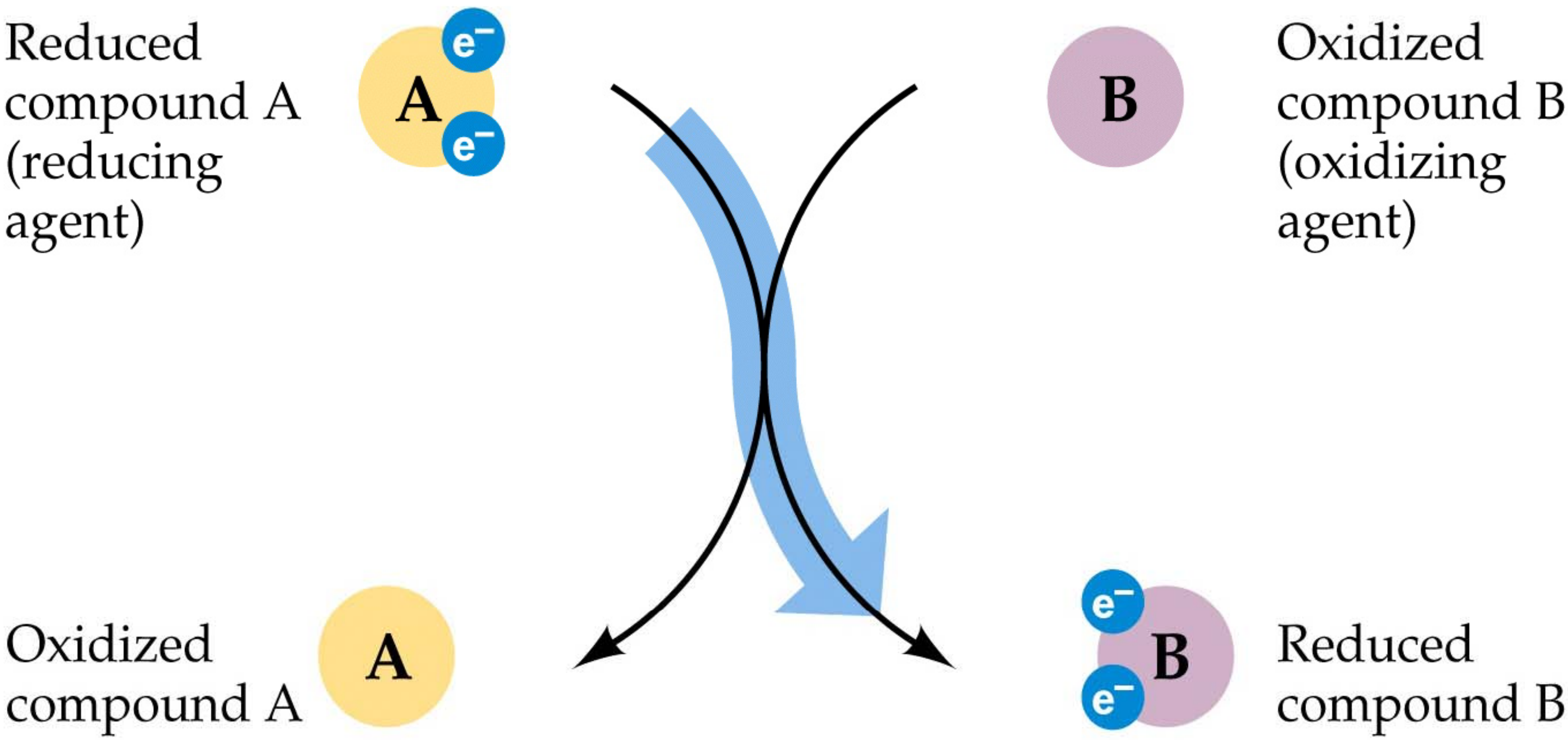


(a) Uncontrolled reaction (b) Cellular respiration

C. Obtaining Energy and Electrons from Glucose

- As a material is oxidized, the electrons it loses transfer to another material, which is thereby reduced.
- Such redox reactions transfer a lot of energy. Much of the energy liberated by the oxidation of the reducing agent is captured in the reduction of the oxidizing agent.

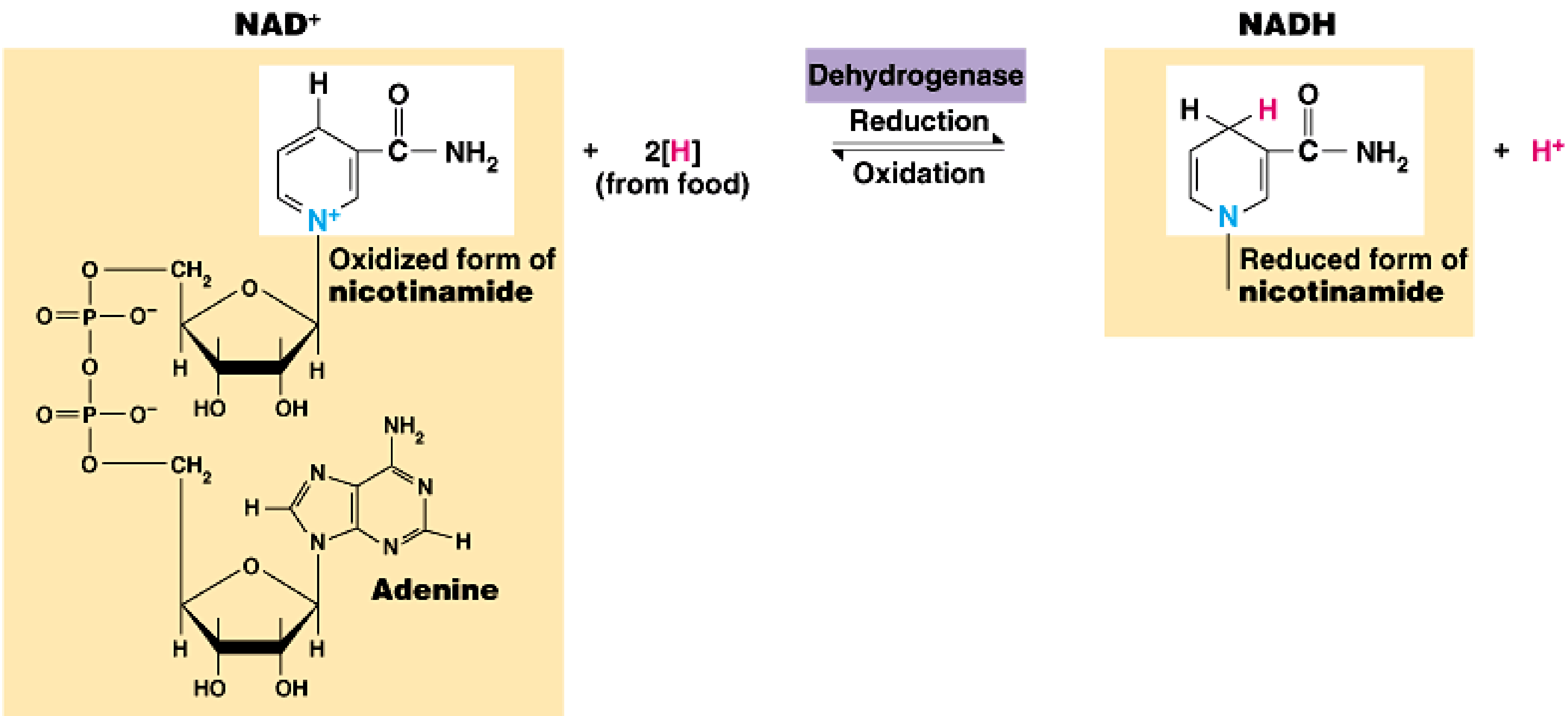
Redox Rxns: Transfer Electrons AND Energy



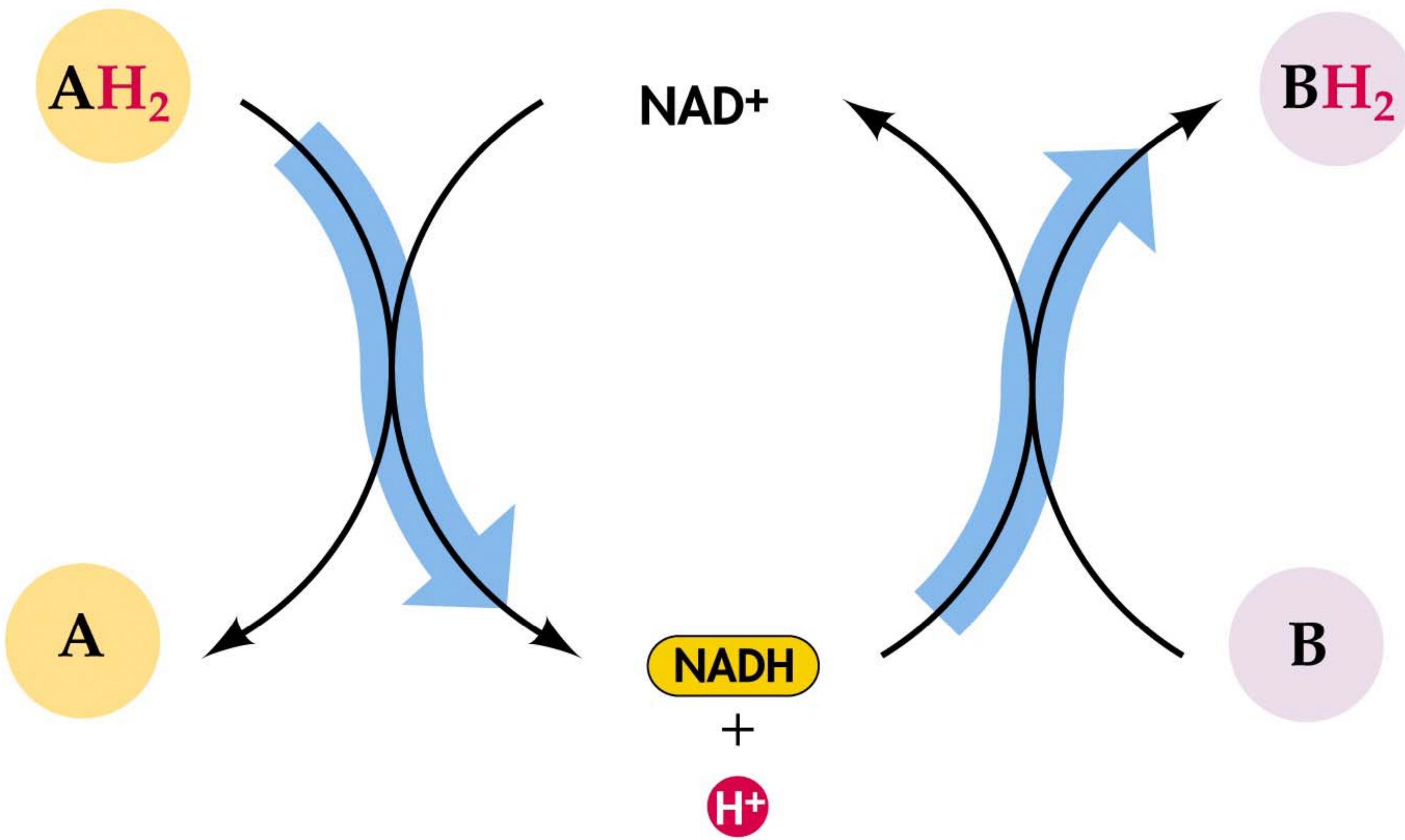
C. Obtaining Energy and Electrons from Glucose

- The coenzyme NAD is a key electron carrier in biological redox reactions.
- It exists in two forms, one oxidized (NAD^+) and the other reduced ($NADH + H^+$).

NAD^+ as an electron shuttle

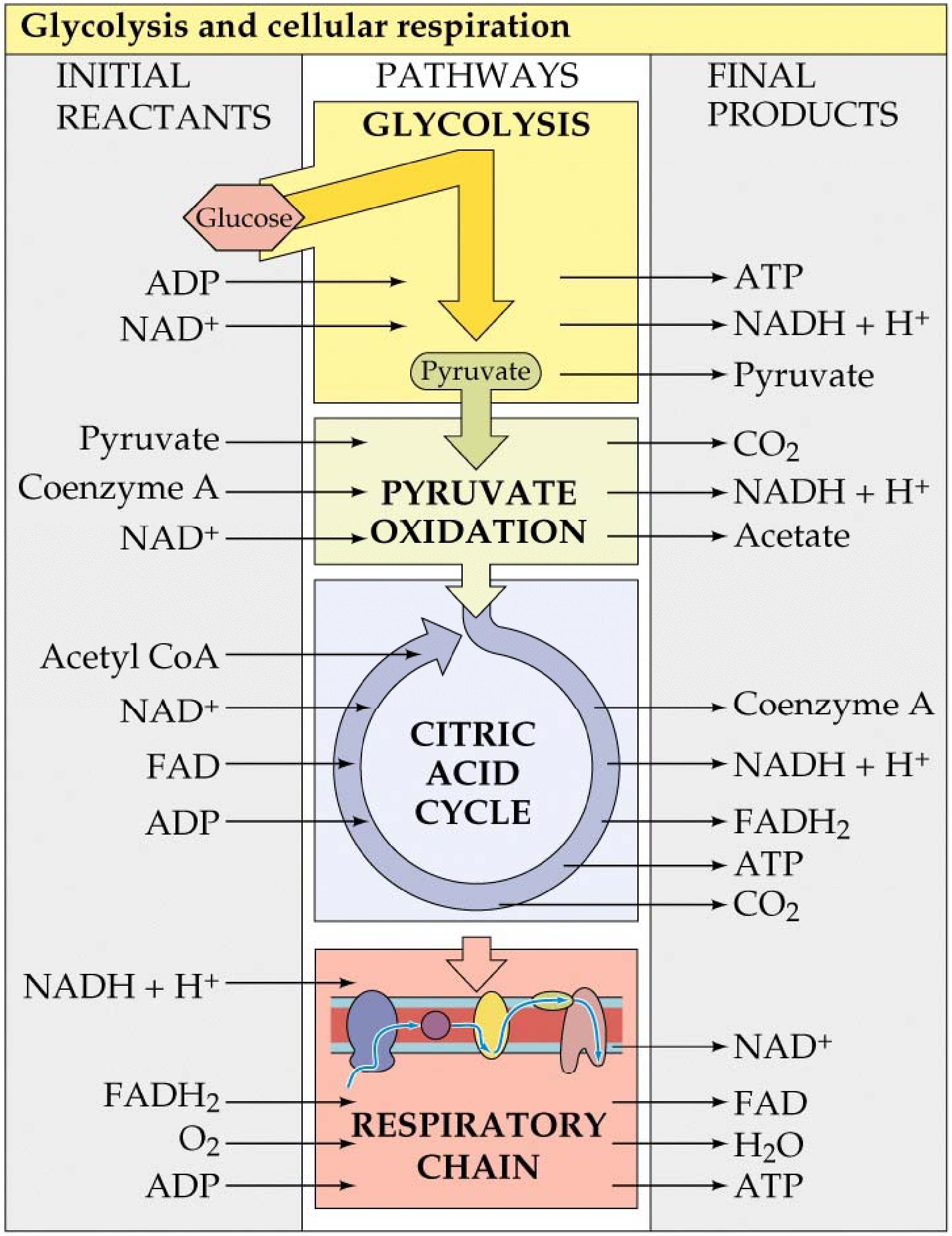


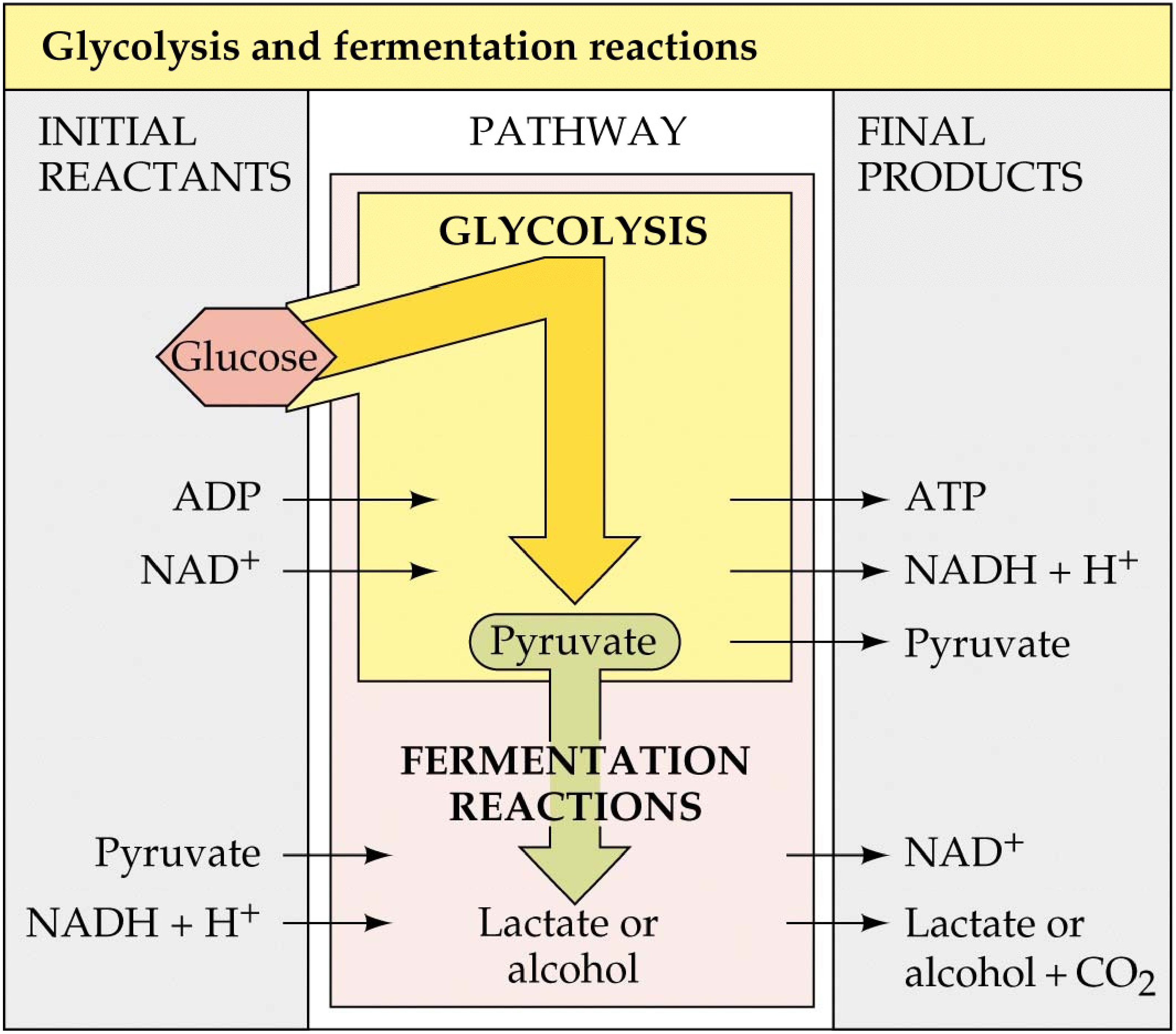
NAD as an Electron Carrier and Redox Couple



D. An Overview: Releasing Energy from Glucose

- Glycolysis operates in the presence or absence of O_2.
- Under aerobic conditions, cellular respiration continues the breakdown process.


Glycolysis and cellular respiration
INITIAL REACTANTS
PATHWAYS
FINAL PRODUCTS
GLYCOLYSIS
Glucose
ADP
NAD^+
ATP
$NADH + H^+$
Pyruvate
Pyruvate
Pyruvate
Coenzyme A
NAD^+
PYRUVATE OXIDATION
CO_2
$NADH + H^+$
Acetate
Acetyl CoA
NAD^+
FAD
ADP
CITRIC ACID CYCLE
Coenzyme A
$NADH + H^+$
$FADH_2$
ATP
CO_2
$NADH + H^+$
$FADH_2$
O_2
ADP
RESPIRATORY CHAIN
NAD^+
FAD
H_2O
ATP


Glycolysis and fermentation reactions
INITIAL REACTANTS
PATHWAY
FINAL PRODUCTS
GLYCOLYSIS
Glucose
ADP
NAD+
ATP
NADH + H+
Pyruvate
Pyruvate
FERMENTATION REACTIONS
Pyruvate
NADH + H+
NAD+
Lactate or alcohol
Lactate or alcohol + CO2

D. An Overview: Releasing Energy from Glucose

- Pyruvate oxidation and the citric acid cycle produce CO_2 and hydrogen atoms carried by NADH and $FADH_2$.
- The respiratory chain combines the hydrogens with O_2, releasing enough energy for additional ATP synthesis.

D. An Overview: Releasing Energy from Glucose

- In some cells under anaerobic conditions, pyruvate can be reduced by NADH to form lactate and regenerate the NAD needed to sustain glycolysis.
- This is called a fermentation.

D. An Overview: Releasing Energy from Glucose

- In eucarya, glycolysis and fermentation occur in the cytoplasm outside of the mitochondria; pyruvate oxidation, the citric acid cycle, and the respiratory chain operate in association with mitochondria.
- In bacteria, glycolysis, fermentation, and the citric acid cycle take place in the cytoplasm; and pyruvate oxidation and the respiratory chain operate in association with the plasma membrane.

7.1 *Cellular Locations for Energy Pathways in Eukaryotes and Prokaryotes*

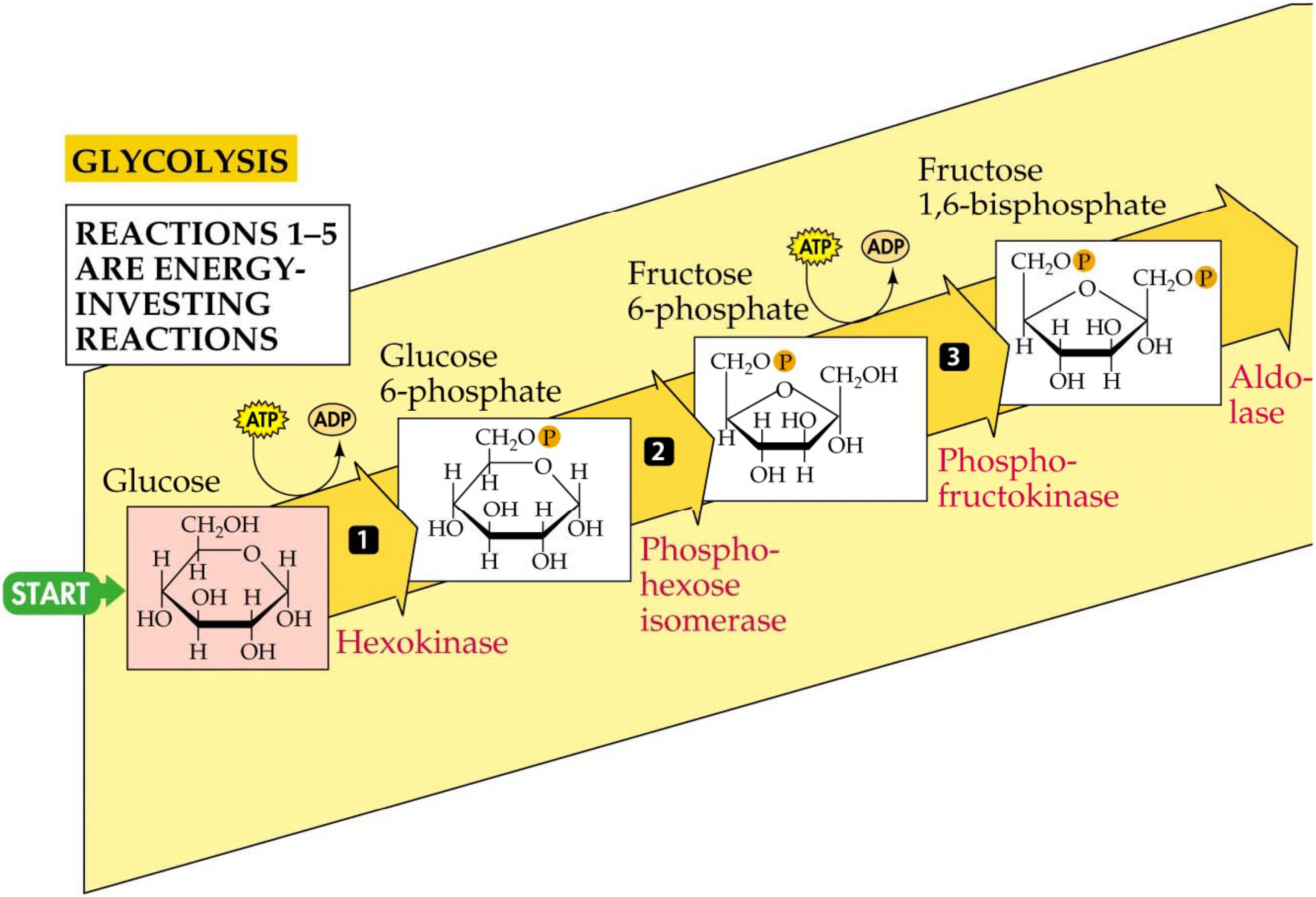
EUKARYOTES	PROKARYOTES
External to mitochondrion	**In cytoplasm**
Glycolysis	Glycolysis
Fermentation	Fermentation
	Citric acid cycle
Inside mitochondrion	**On inner face of plasma membrane**
Inner membrane	Pyruvate oxidation
Pyruvate oxidation	Respiratory chain
Respiratory chain	
Matrix	
Citric acid cycle	

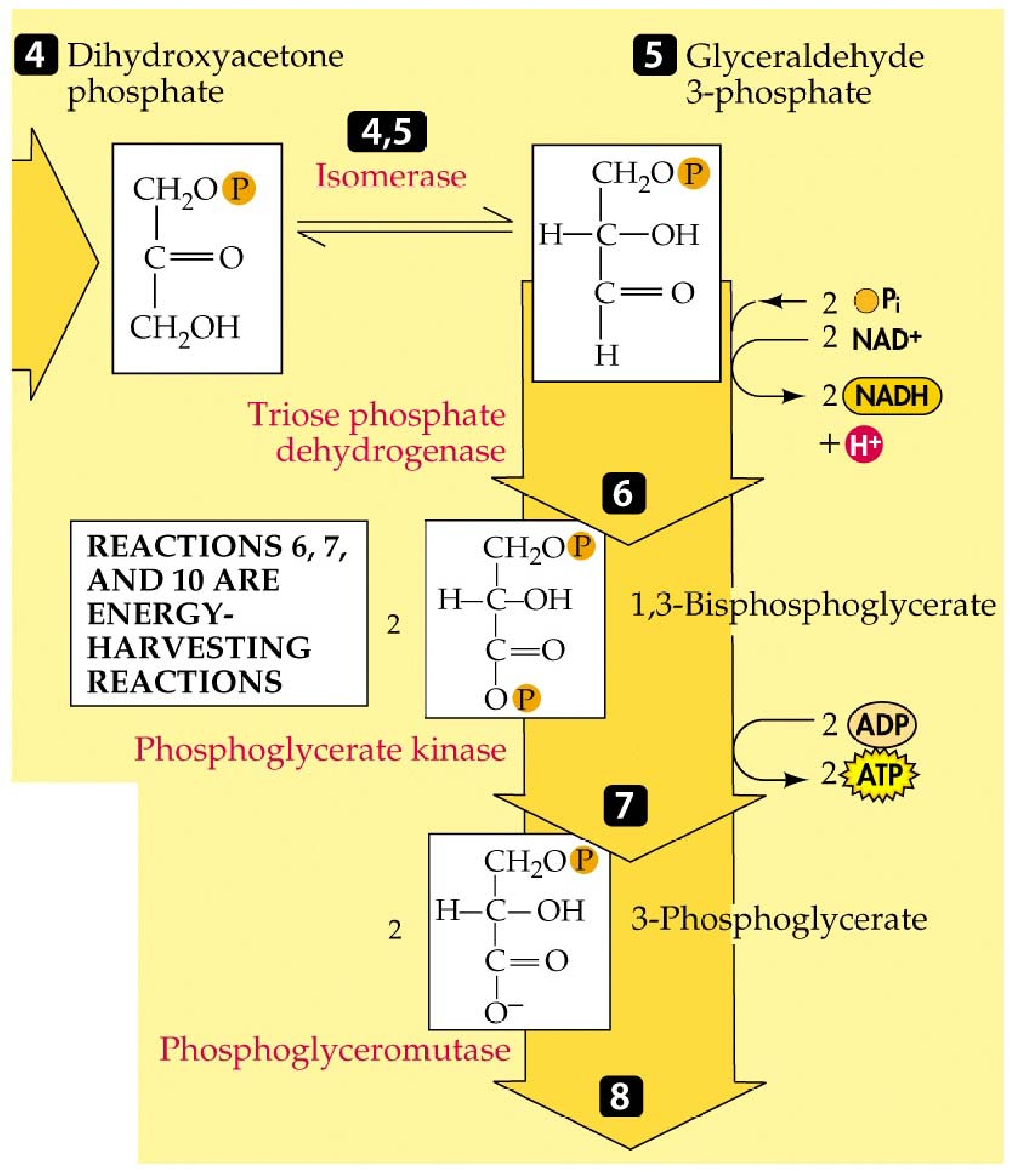
E. Glycolysis: From Glucose to Pyruvate

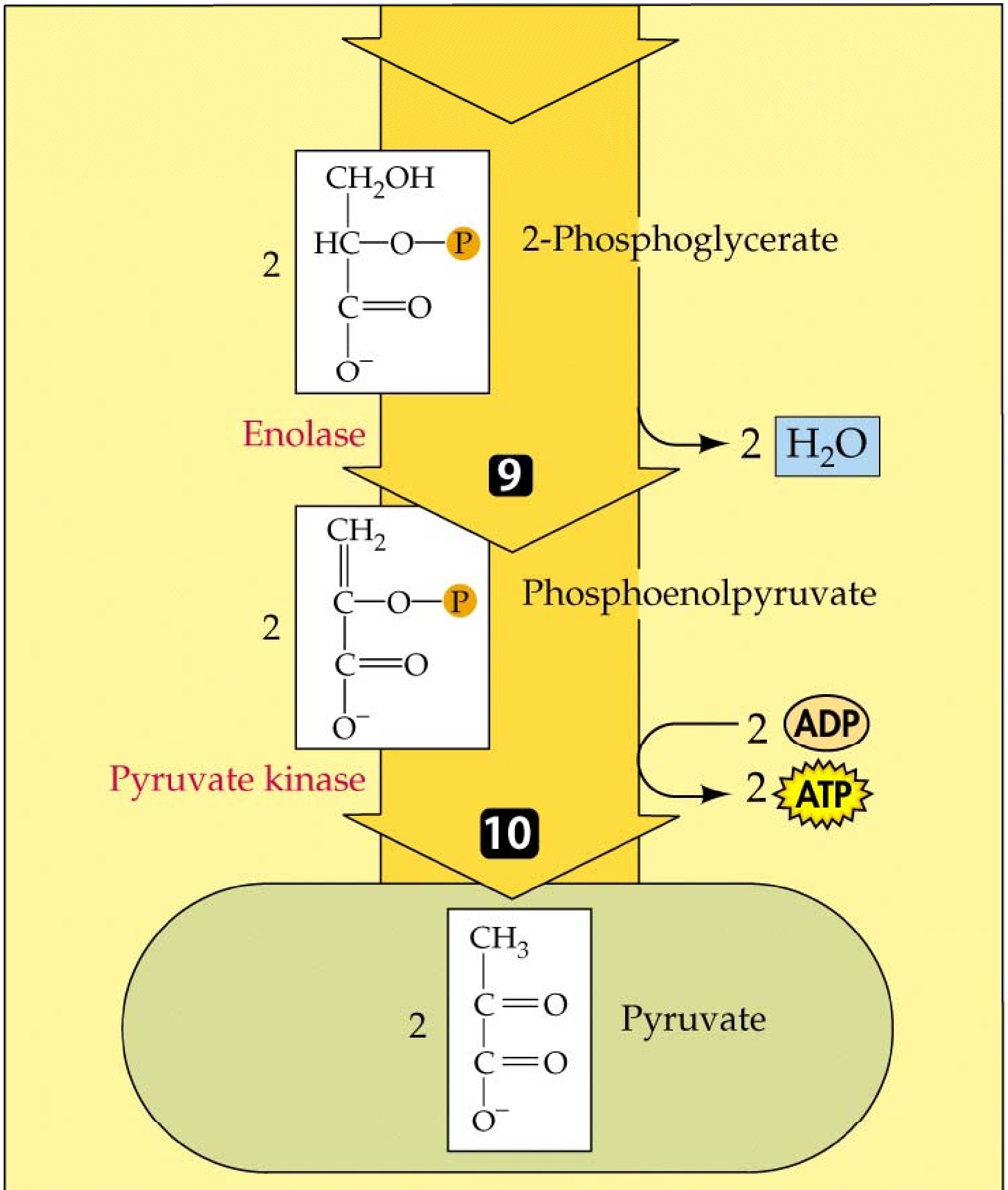
- Glycolysis is a pathway of ten enzyme-catalyzed reactions located in the cytoplasm.
- It provides starting materials for both cellular respiration and fermentation.

E. Glycolysis: From Glucose to Pyruvate

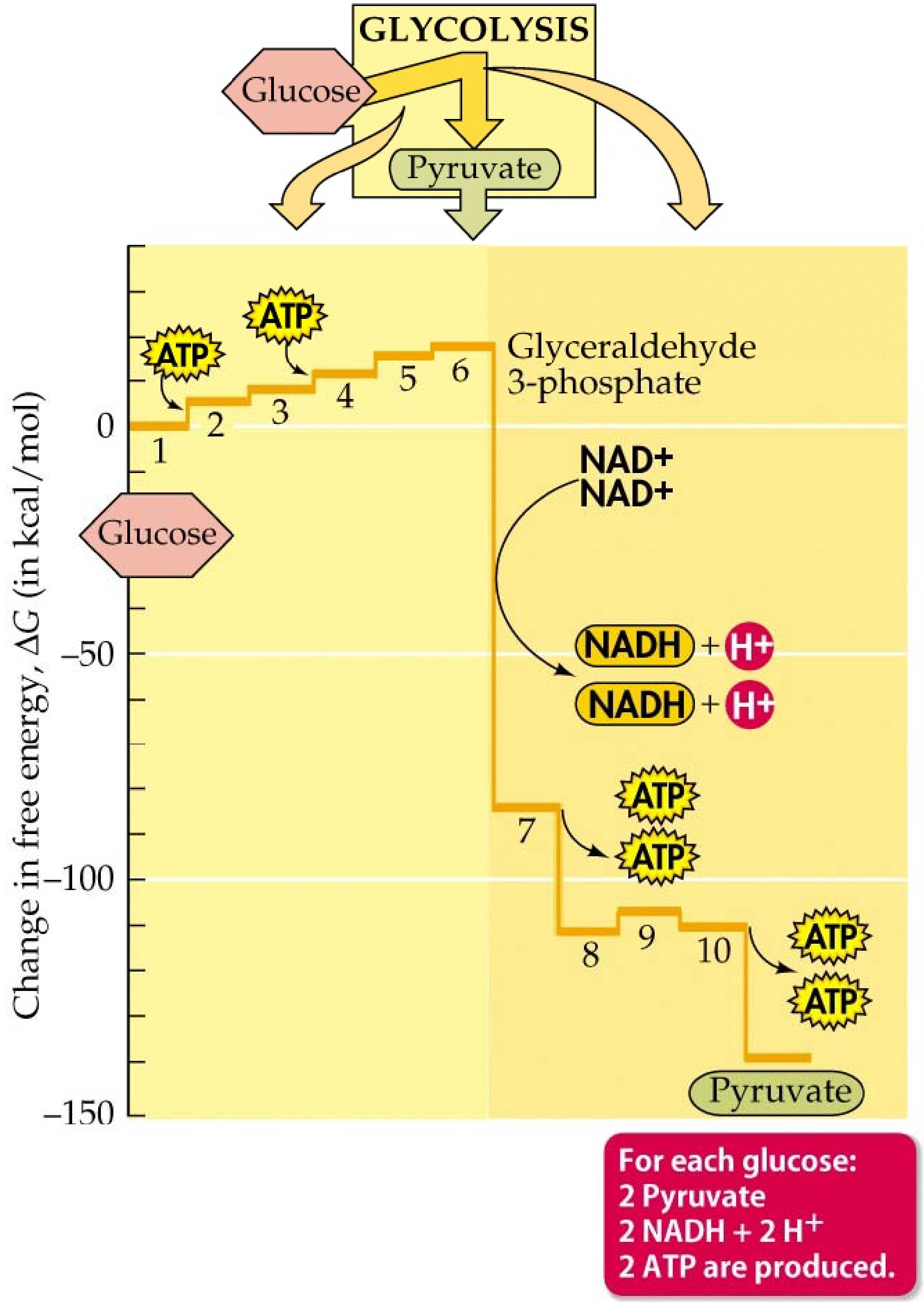
- The energy-investing reactions of glycolysis use two ATPs per glucose molecule and eventually yield two glyceraldehyde 3-phosphate molecules.
- In the energy-harvesting reactions, two NADH molecules are produced, and four ATP molecules are generated by substrate-level phosphorylation.
- Two pyruvates are produced for each glucose molecule.


GLYCOLYSIS
REACTIONS 1–5 ARE ENERGY-INVESTING REACTIONS
START
Glucose
ATP
ADP
1
Hexokinase
Glucose 6-phosphate
2
Phospho-hexose isomerase
Fructose 6-phosphate
ATP
ADP
3
Phospho-fructokinase
Fructose 1,6-bisphosphate
Aldo-lase

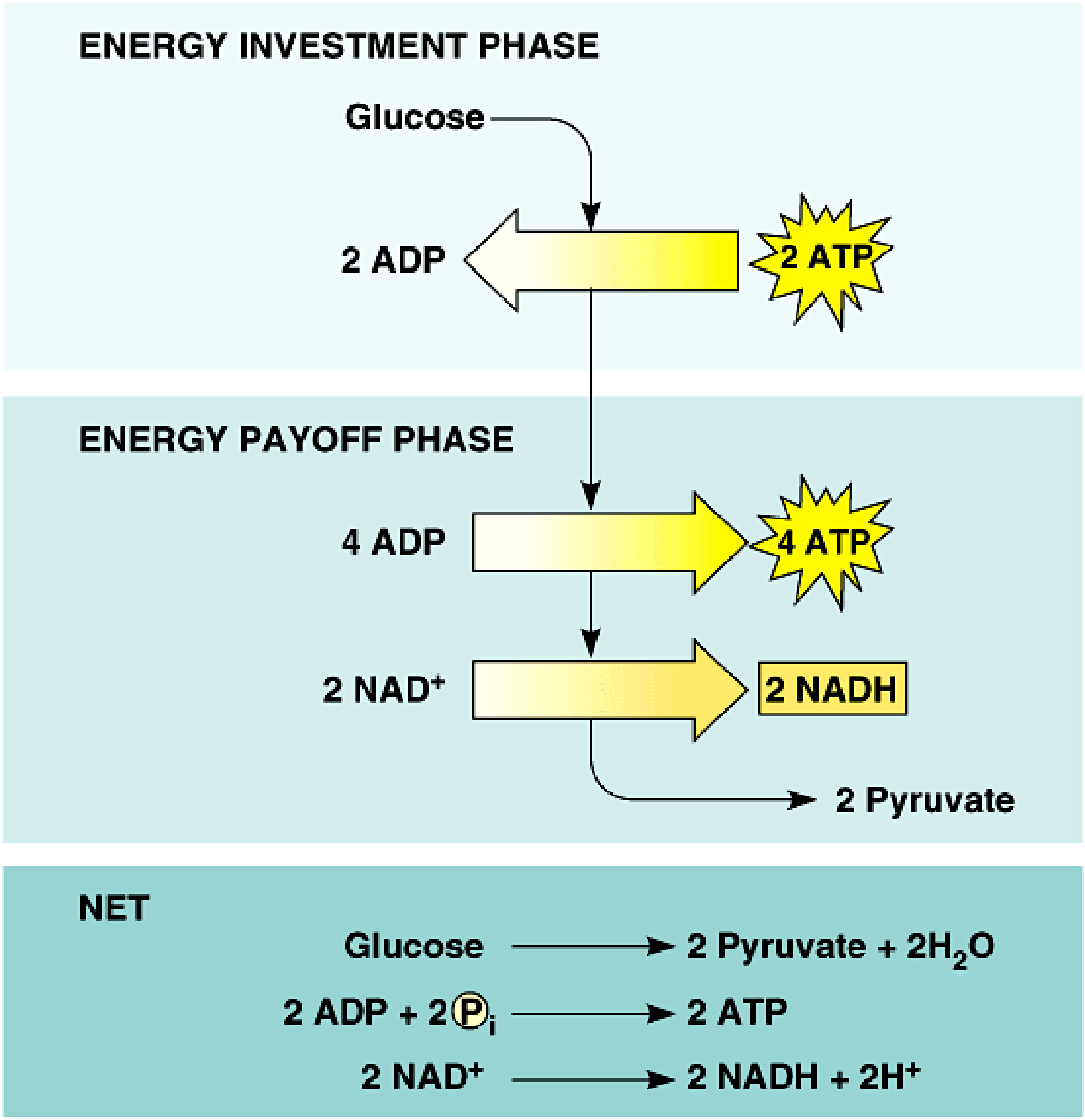

4 Dihydroxyacetone phosphate
5 Glyceraldehyde 3-phosphate
4,5
Isomerase
Triose phosphate dehydrogenase
2 Pi
2 NAD+
2 NADH
+ H+
6
REACTIONS 6, 7, AND 10 ARE ENERGY-HARVESTING REACTIONS
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
2 ADP
2 ATP
7
3-Phosphoglycerate
Phosphoglyceromutase
8



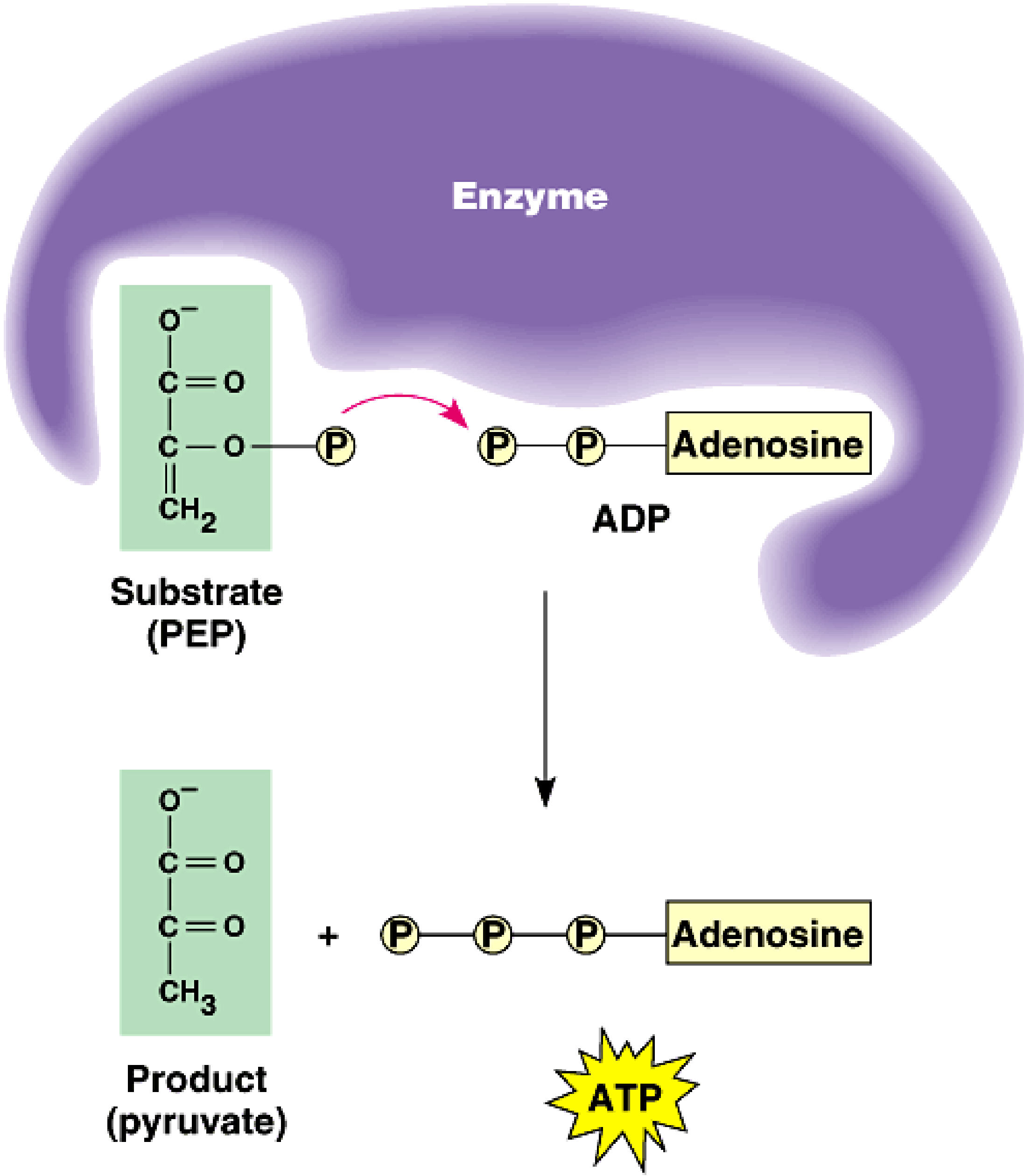
Glycolysis nets two molecules of ATP and two molecules of the electron carrier NADH. Two molecules of pyruvate are produced.


GLYCOLYSIS
Glucose
Pyruvate
Change in free energy, ΔG (in kcal/mol)
0
−50
−100
−150
ATP
ATP
1
2
3
4
5
6
Glyceraldehyde 3-phosphate
Glucose
NAD+
NAD+
NADH + H+
NADH + H+
7
ATP
ATP
8
9
10
ATP
ATP
Pyruvate
For each glucose:
2 Pyruvate
2 NADH + 2 H+
2 ATP are produced.

The energy input and output of glycolysis



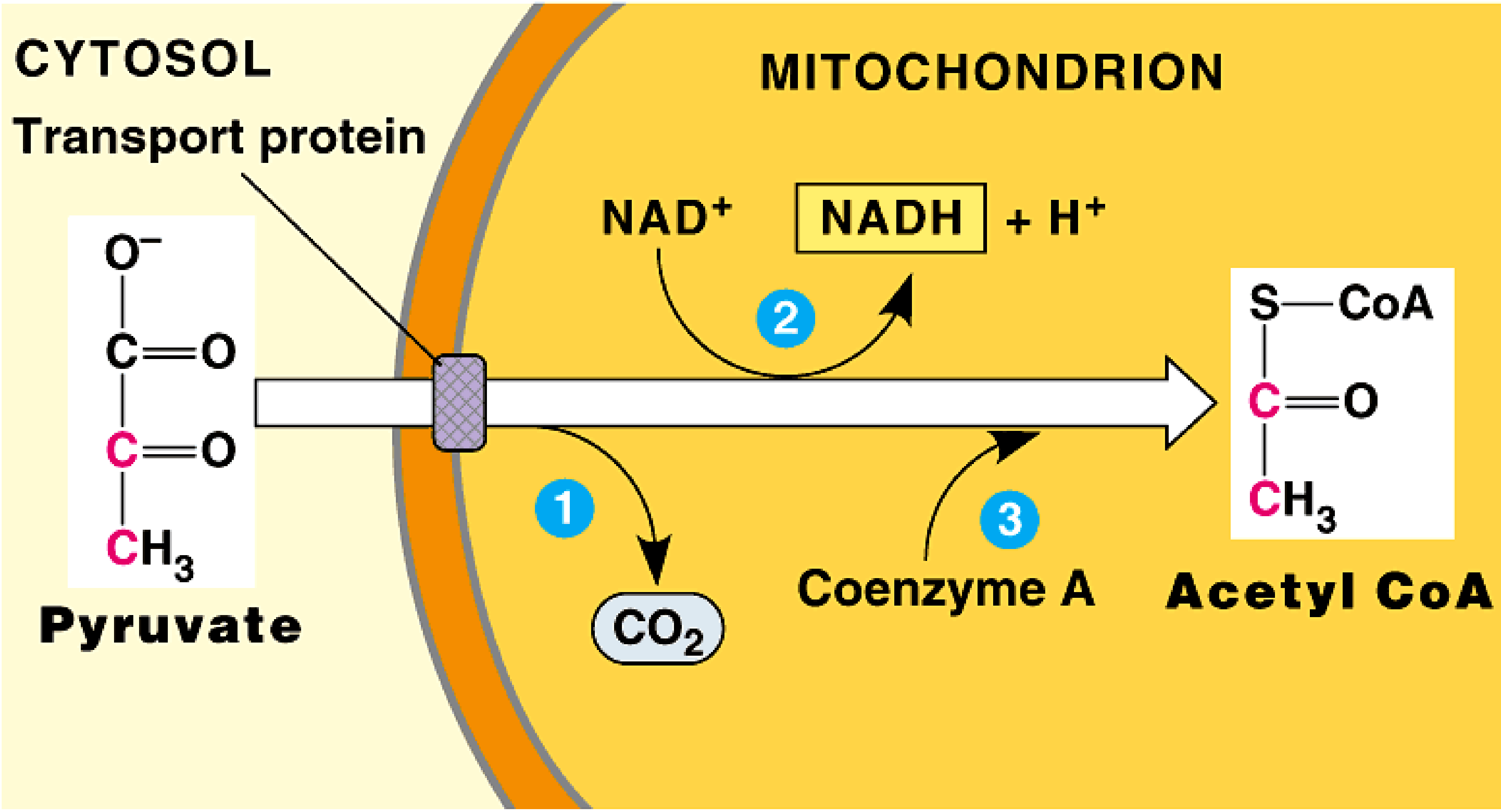
Substrate-level phosphorylation

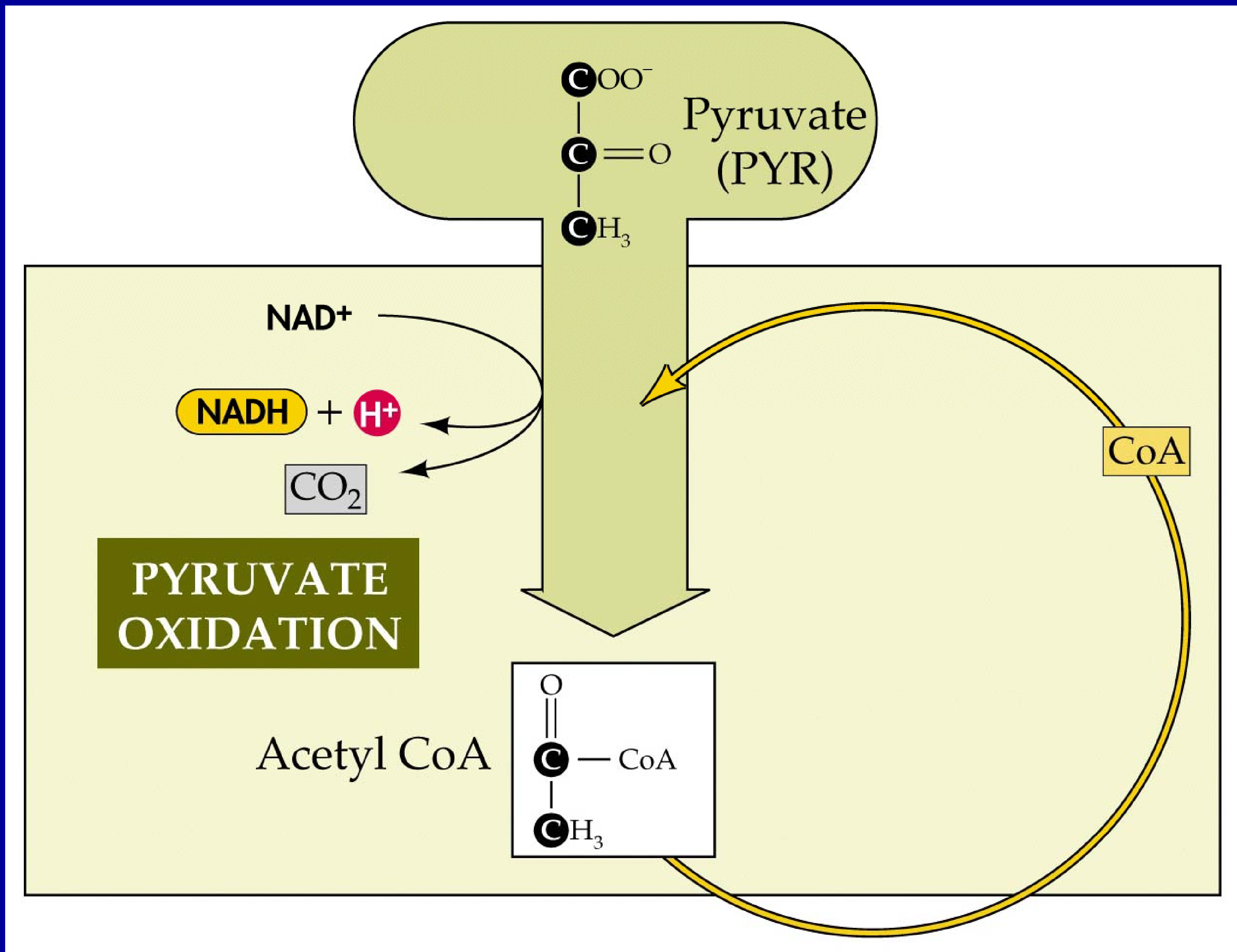


F. Pyruvate Oxidation

- The pyruvate dehydrogenase complex catalyzes three reactions:
- (1) Pyruvate is oxidized to the acetyl group, releasing one CO_2 molecule and energy;
- (2) some of this energy is captured when NAD^+ is reduced to $NADH + H^+$; and
- (3) the remaining energy is captured when the acetyl group combines with coenzyme A, yielding acetyl CoA.

Conversion of pyruvate to acetyl CoA, the junction between glycolysis and the Krebs aka Citric Acid Cycle

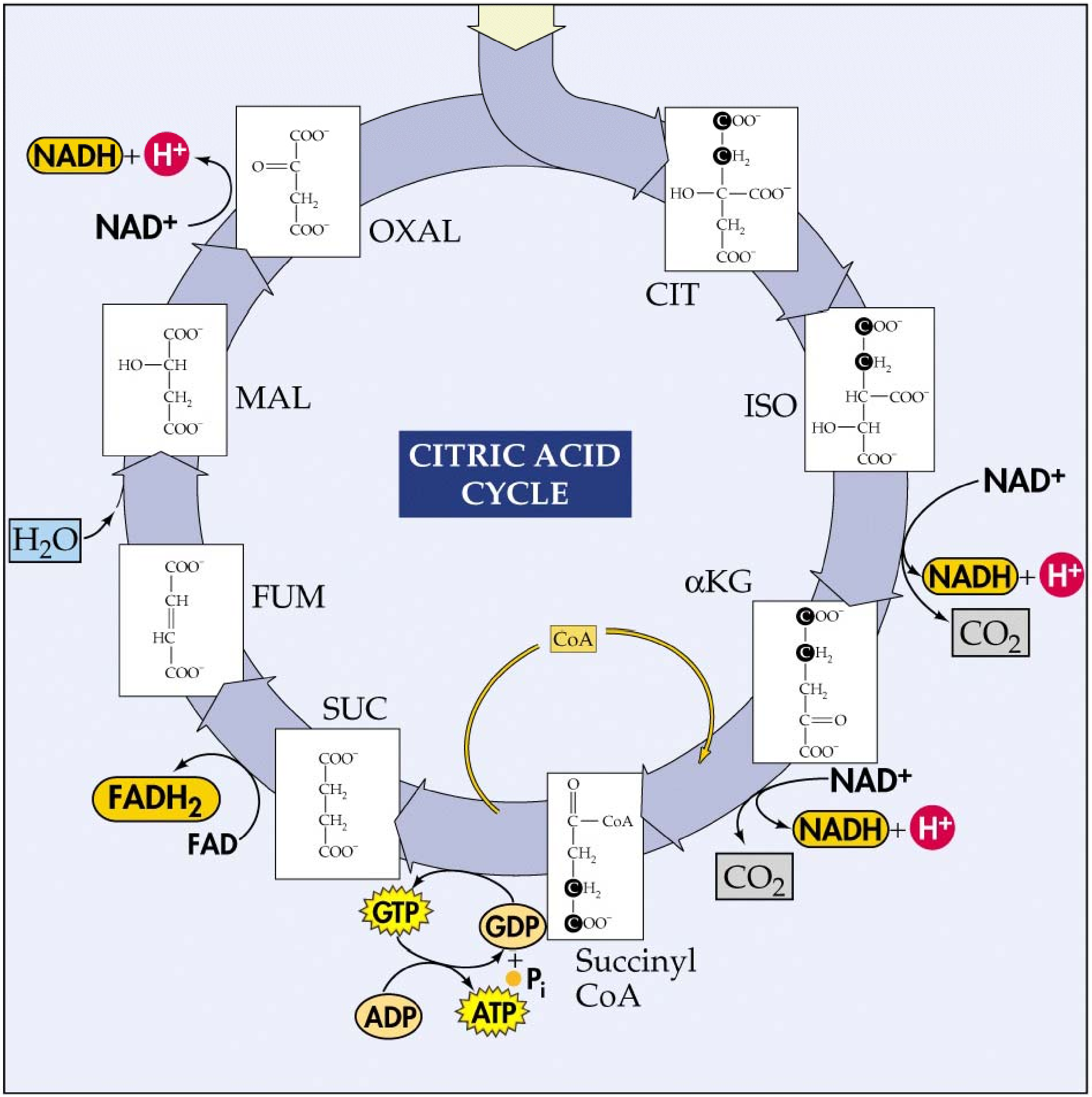


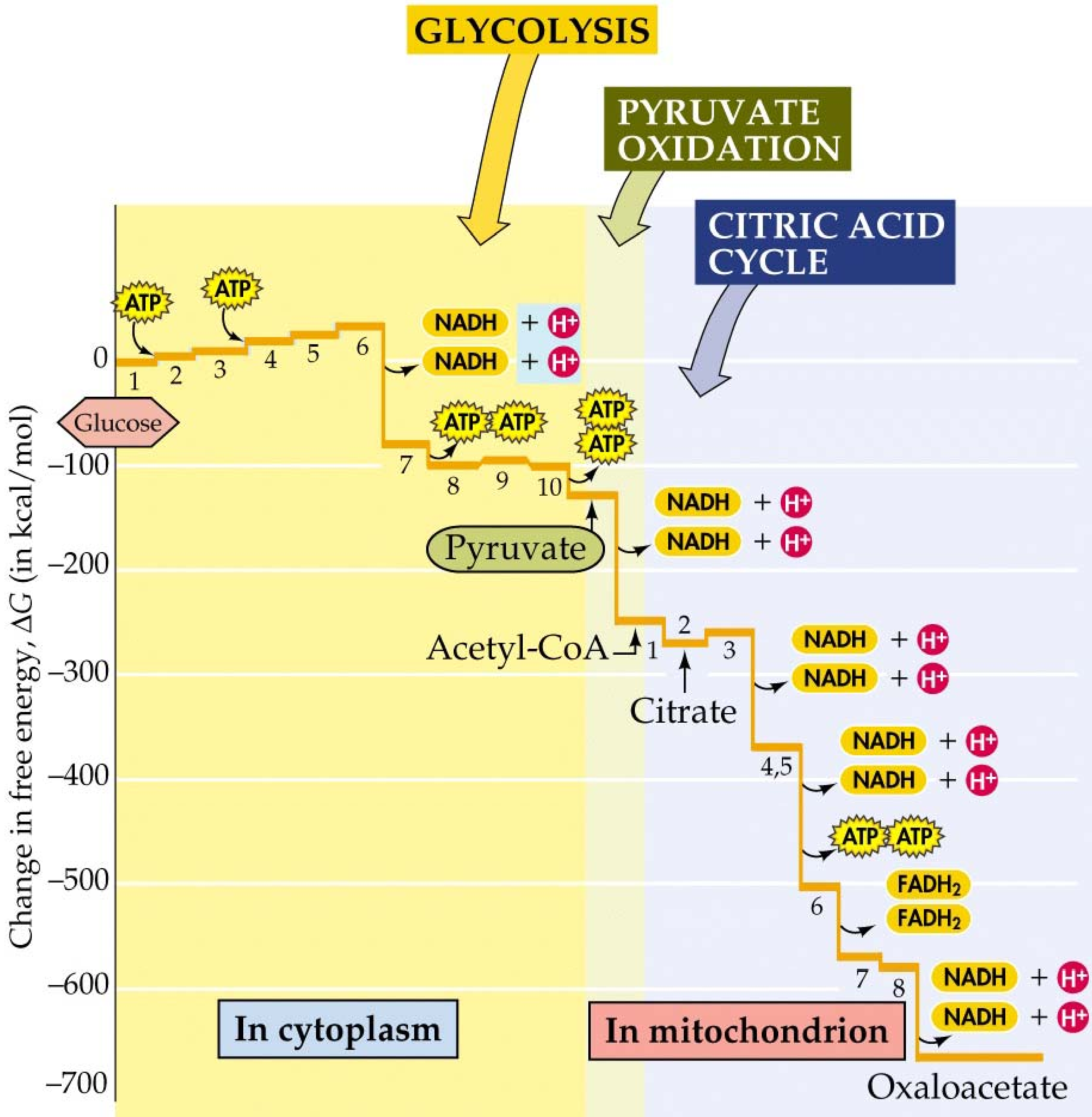


COO⁻
C=O
CH3
Pyruvate (PYR)
NAD+
NADH + H+
CO2
PYRUVATE OXIDATION
CoA
Acetyl CoA
O
C — CoA
CH3

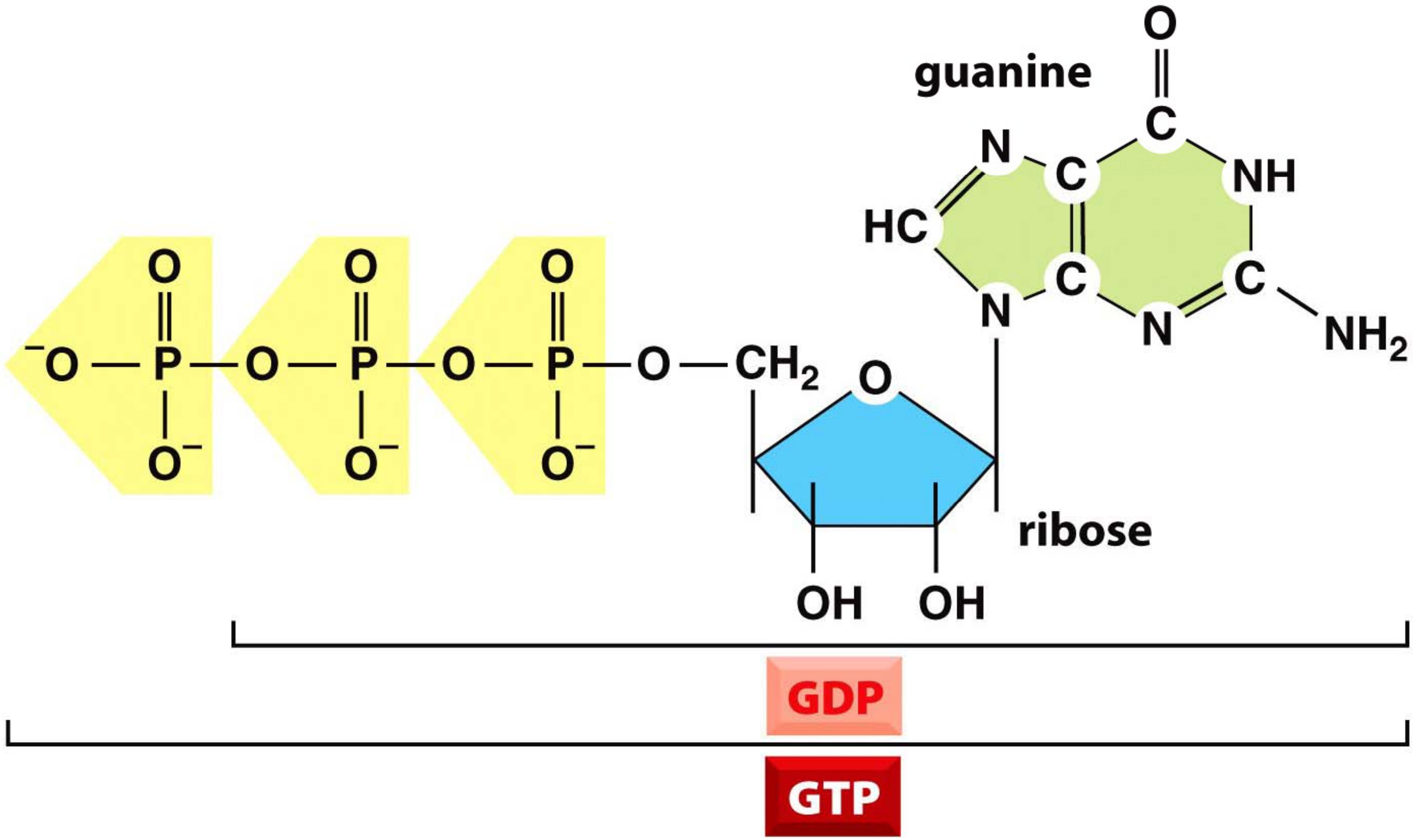
G. The Citric Acid Cycle

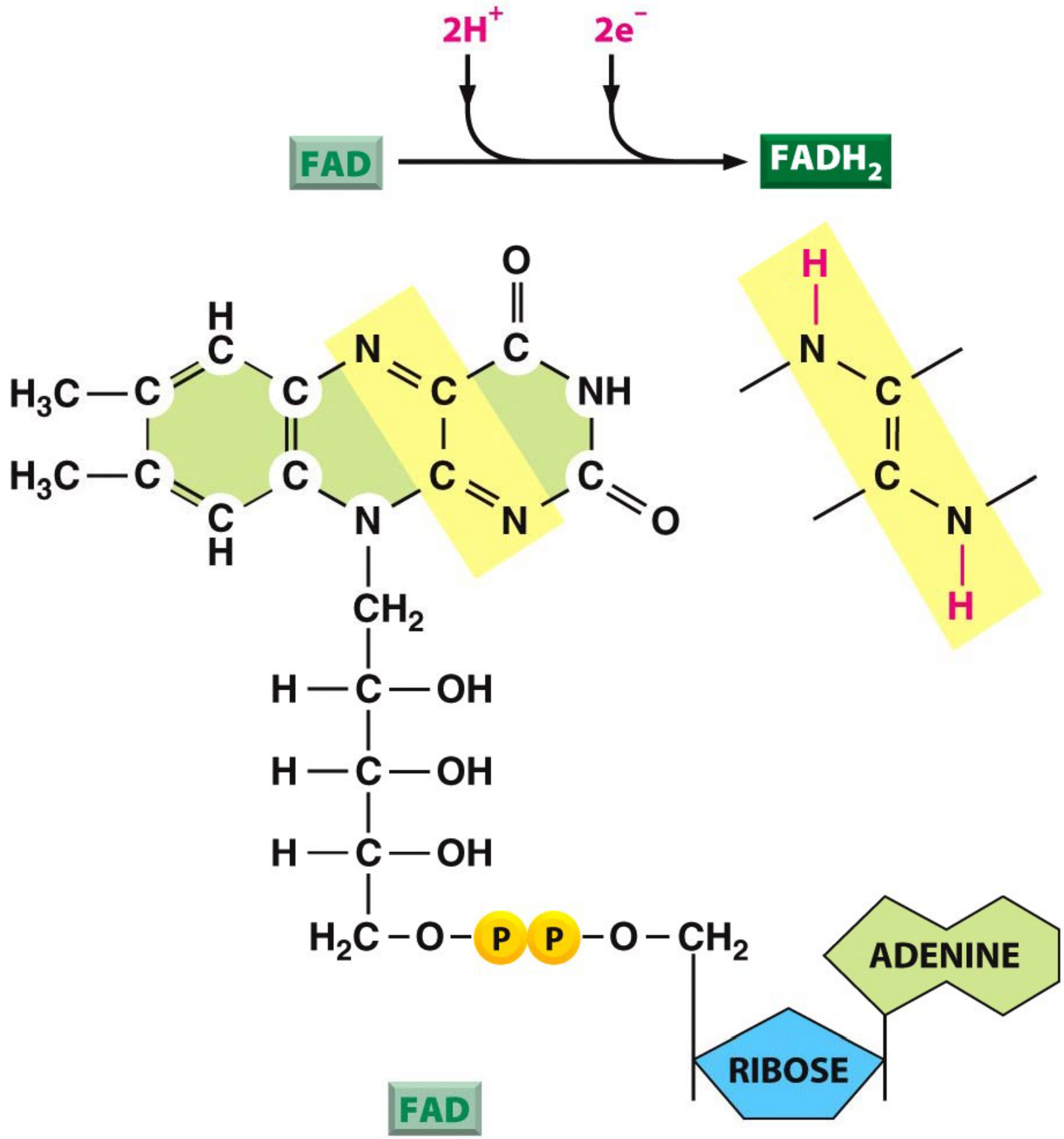
- The energy in acetyl CoA drives the reaction of acetate with oxaloacetate to produce citrate.
- The citric acid cycle is a series of reactions in which citrate is oxidized and oxaloacetate regenerated.
- It produces two CO_2 , one $FADH_2$, three NADH, and one ATP for each acetyl CoA.


CITRIC ACID CYCLE
OXAL
CIT
ISO
αKG
Succinyl CoA
SUC
FUM
MAL
NAD+
NADH + H+
CO2
CoA
GTP
GDP
+ Pi
ADP
ATP
FADH2
FAD
H2O



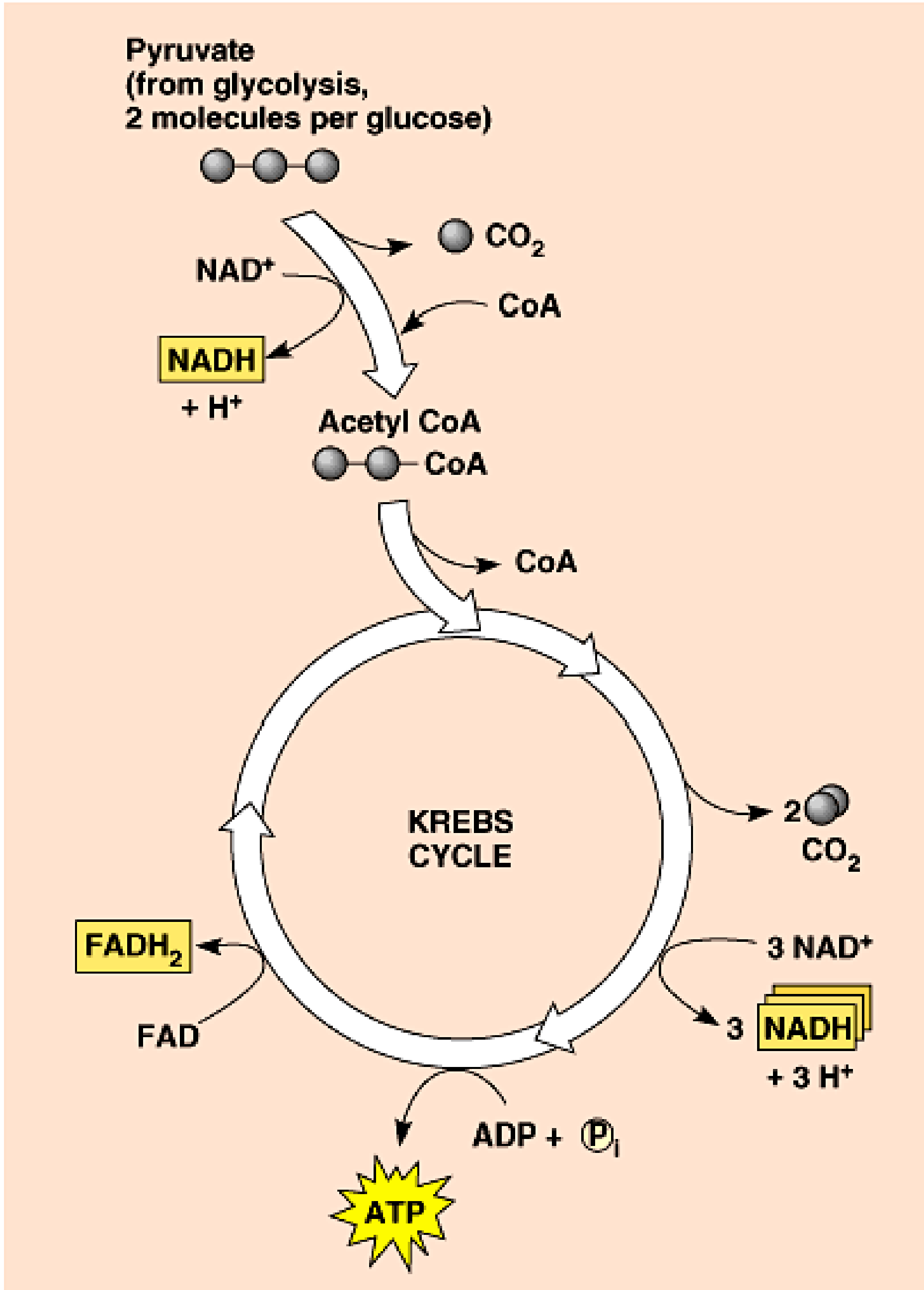
GLYCOLYSIS
PYRUVATE OXIDATION
CITRIC ACID CYCLE
Change in free energy, ΔG (in kcal/mol)
0
–100
–200
–300
–400
–500
–600
–700
Glucose
ATP
ATP
1
2
3
4
5
6
NADH + H+
NADH + H+
7
8
9
10
ATP
ATP
ATP
ATP
Pyruvate
NADH + H+
NADH + H+
Acetyl-CoA
1
2
3
Citrate
NADH + H+
NADH + H+
4,5
NADH + H+
NADH + H+
ATP
ATP
6
FADH2
FADH2
7
8
NADH + H+
NADH + H+
Oxaloacetate
In cytoplasm
In mitochondrion


guanine
ribose
GDP
GTP



2H+
2e−
FAD
FADH2
H
C
H3C
H3C
N
O
NH
O
CH2
H — C — OH
H — C — OH
H — C — OH
H2C − O − P P − O − CH2
ADENINE
RIBOSE
FAD

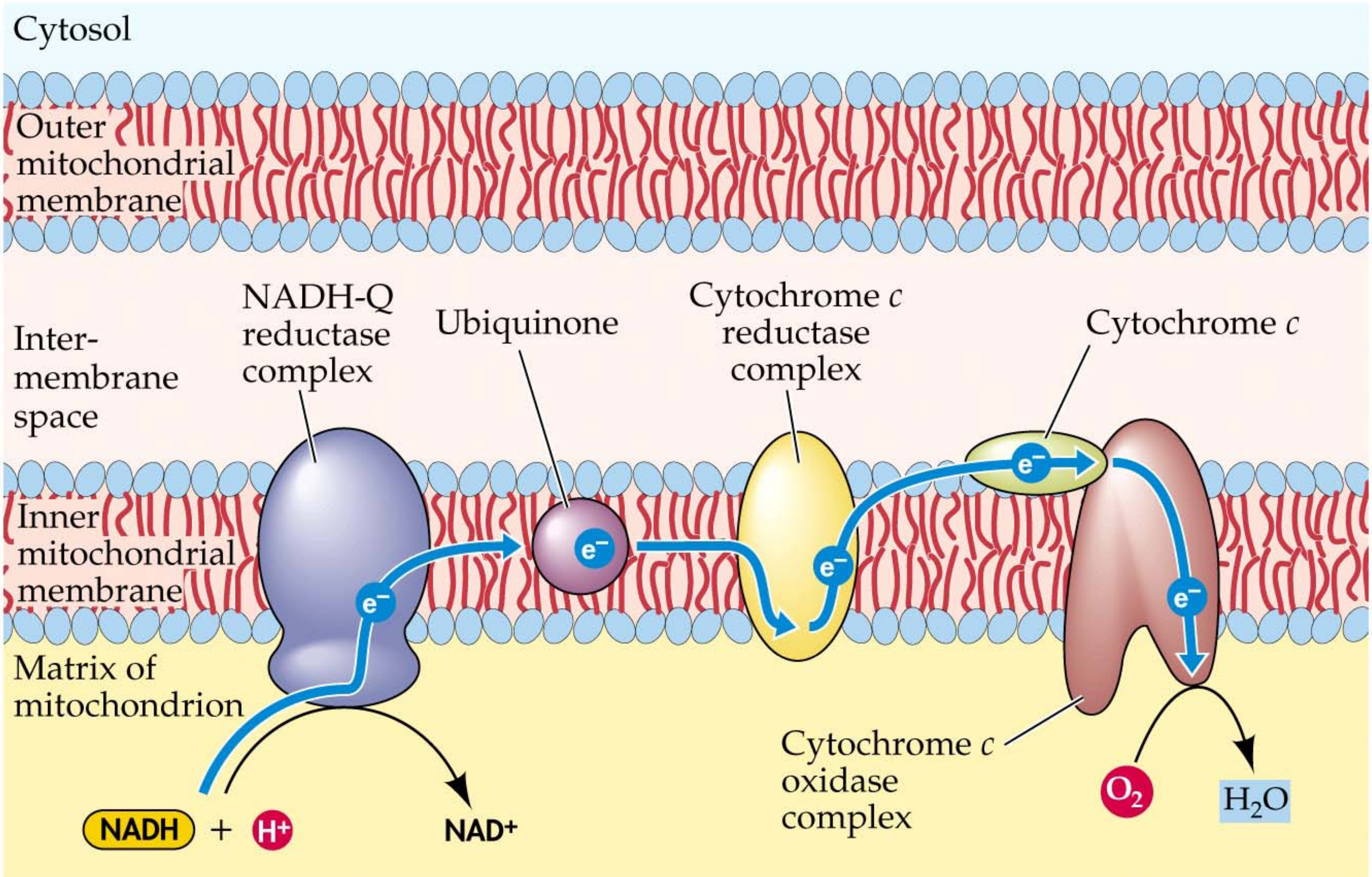
A summary of the Citric Acid Cycle



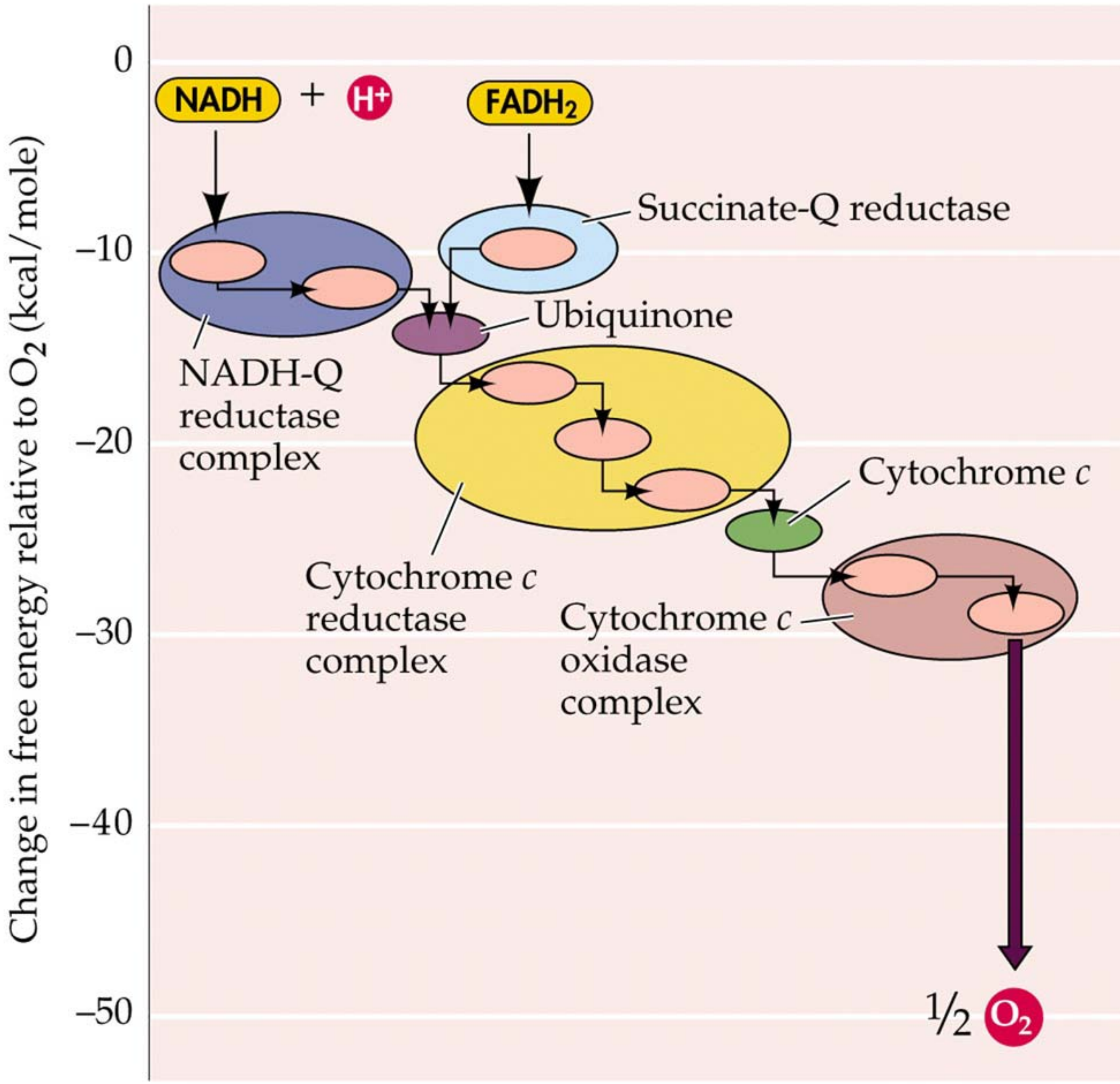
H. The Respiratory Chain: Electrons, Proton Pumping, and ATP

- NADH + H^+ and $FADH_2$ from glycolysis, pyruvate oxidation, and the citric acid cycle are oxidized by the respiratory chain, regenerating NAD^+ and FAD.
- Most of the enzymes and other electron carriers of the chain are part of the inner mitochondrial membrane.
- O_2 is the final acceptor of electrons and protons, forming H_2O.

The Oxidation of NADH + H^+



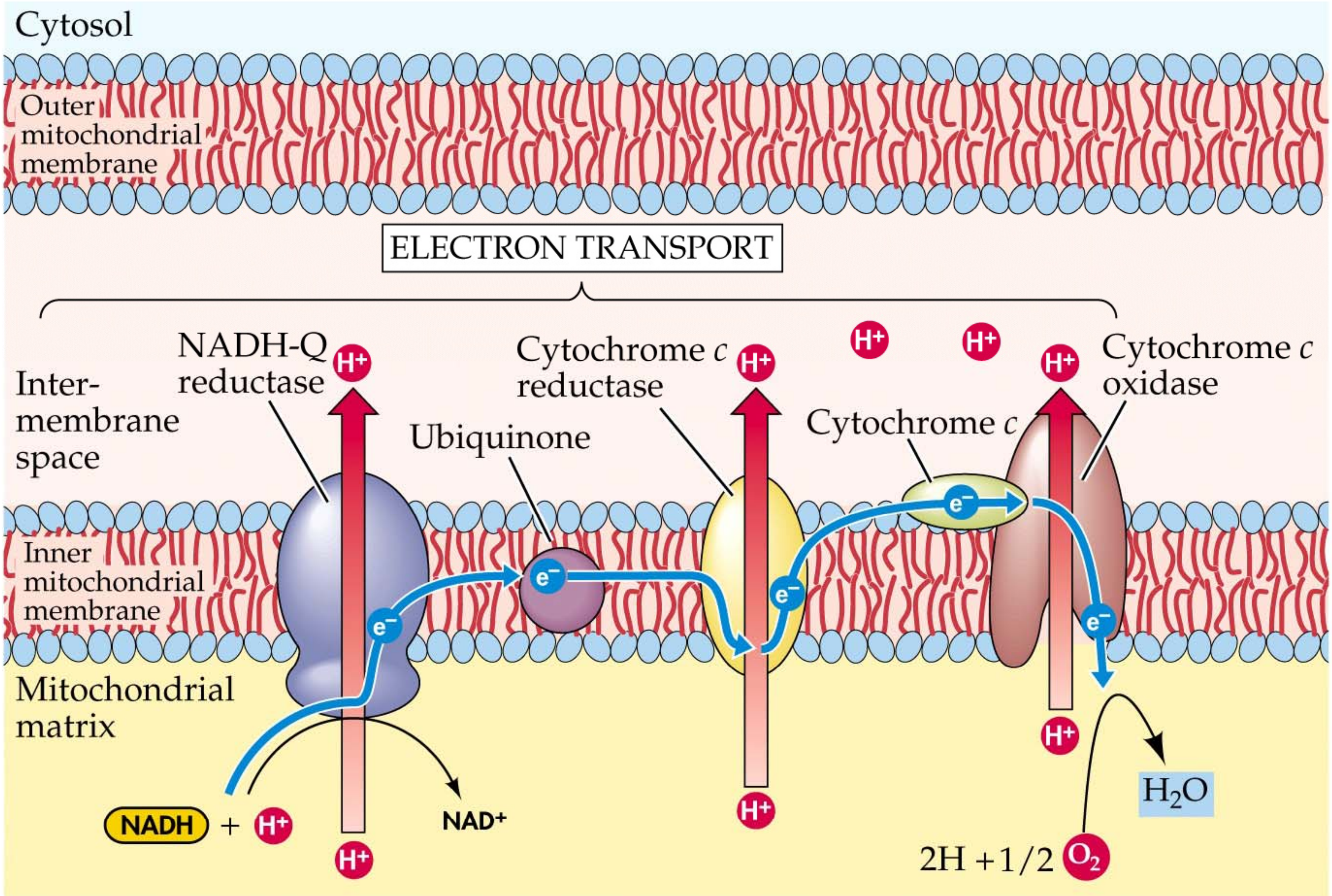
The Complete Respiratory Chain



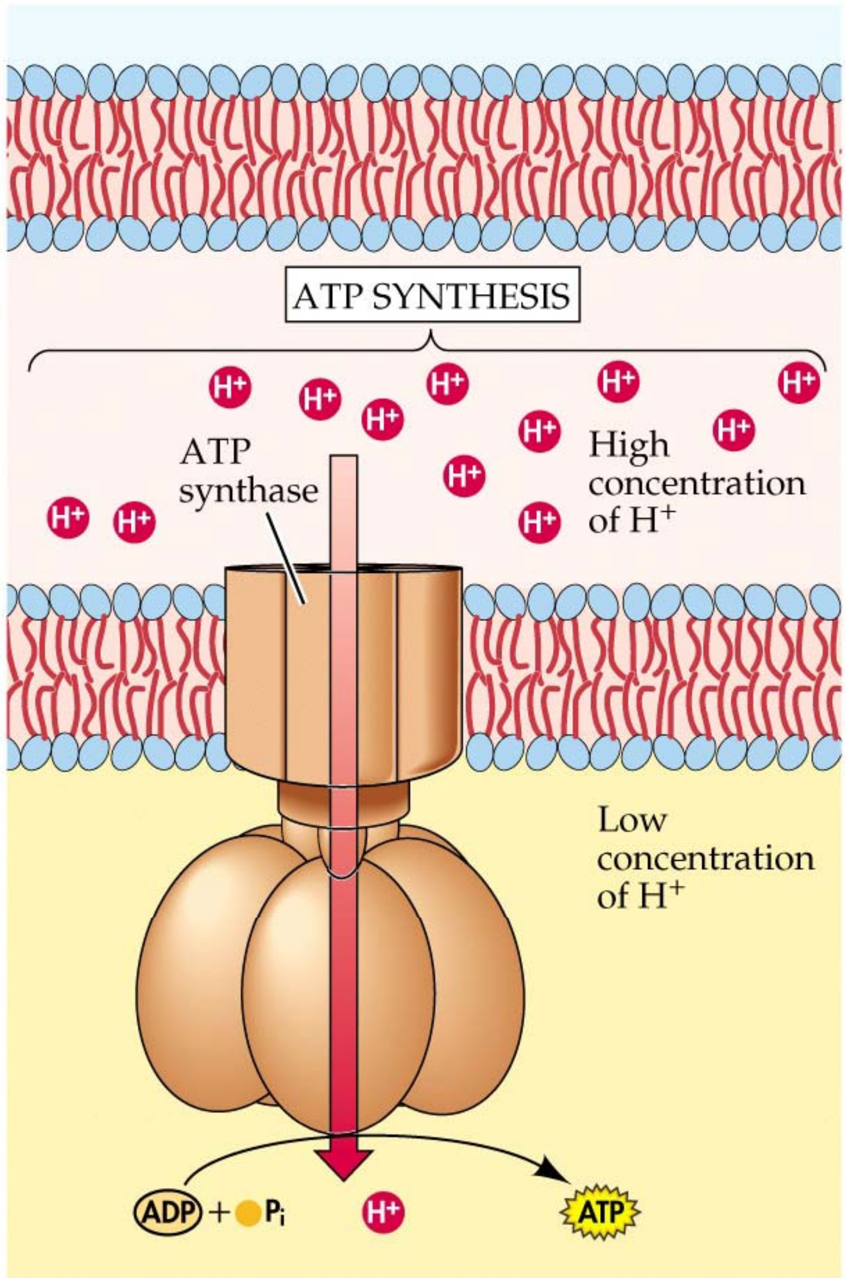
H. The Respiratory Chain: Electrons, Proton Pumping, and ATP

- The chemiosmotic mechanism couples proton transport to oxidative phosphorylation.
- As the electrons move along the respiratory chain, they lose energy, captured by proton pumps that actively transport H^+ out of the mitochondrial matrix, establishing a gradient of proton concentration and electric charge: the proton-motive force or PMF.

The Chemiosmotic Mechanism Produces ATP



The Chemiosmotic Mechanism Produces ATP



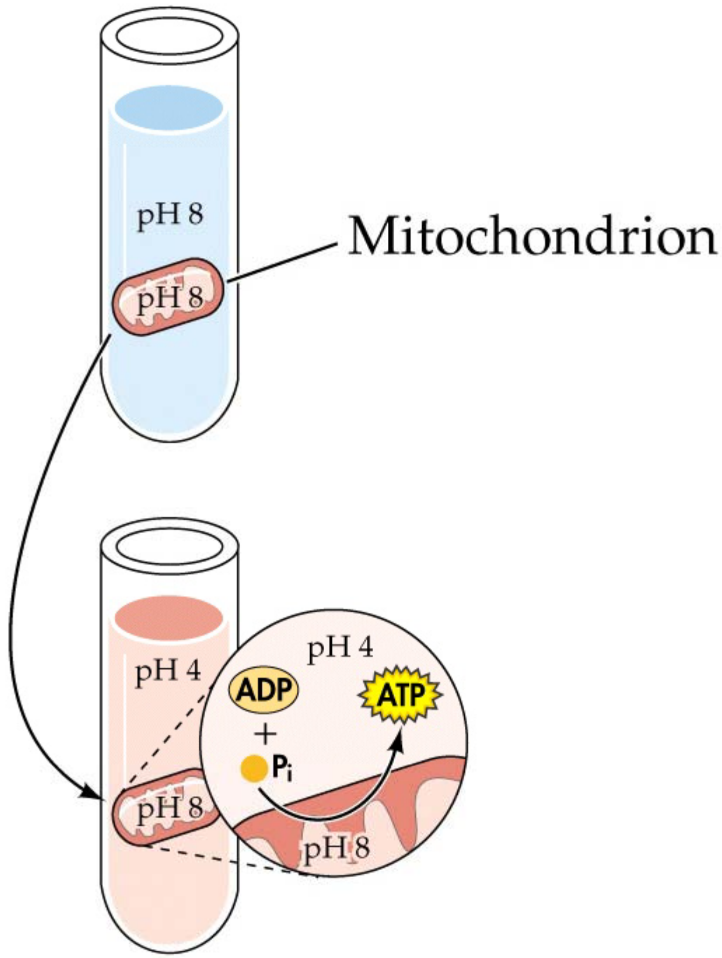
"OxPhos" ATP synthesis

H. The Respiratory Chain: Electrons, Proton Pumping, and ATP

- The proton-motive force causes protons to diffuse back into the mitochondrial interior through the membrane channel protein ATP synthase, which couples that diffusion to the production of ATP.
- Several key experiments demonstrate that it is chemiosmosis that produces ATP.

EXPERIMENT 1

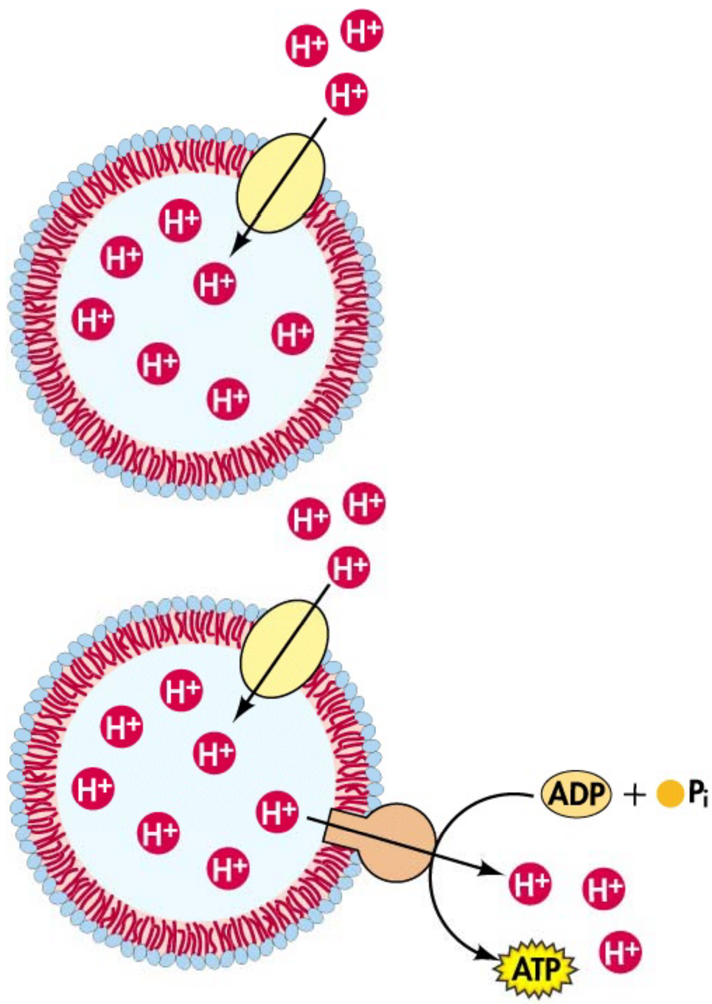
Question: Can an H^+ gradient drive ATP synthesis by isolated mitochondria?



Conclusion: In the absence of electron transport, an artificial H^+ gradient is sufficient for ATP synthesis by mitochondria.

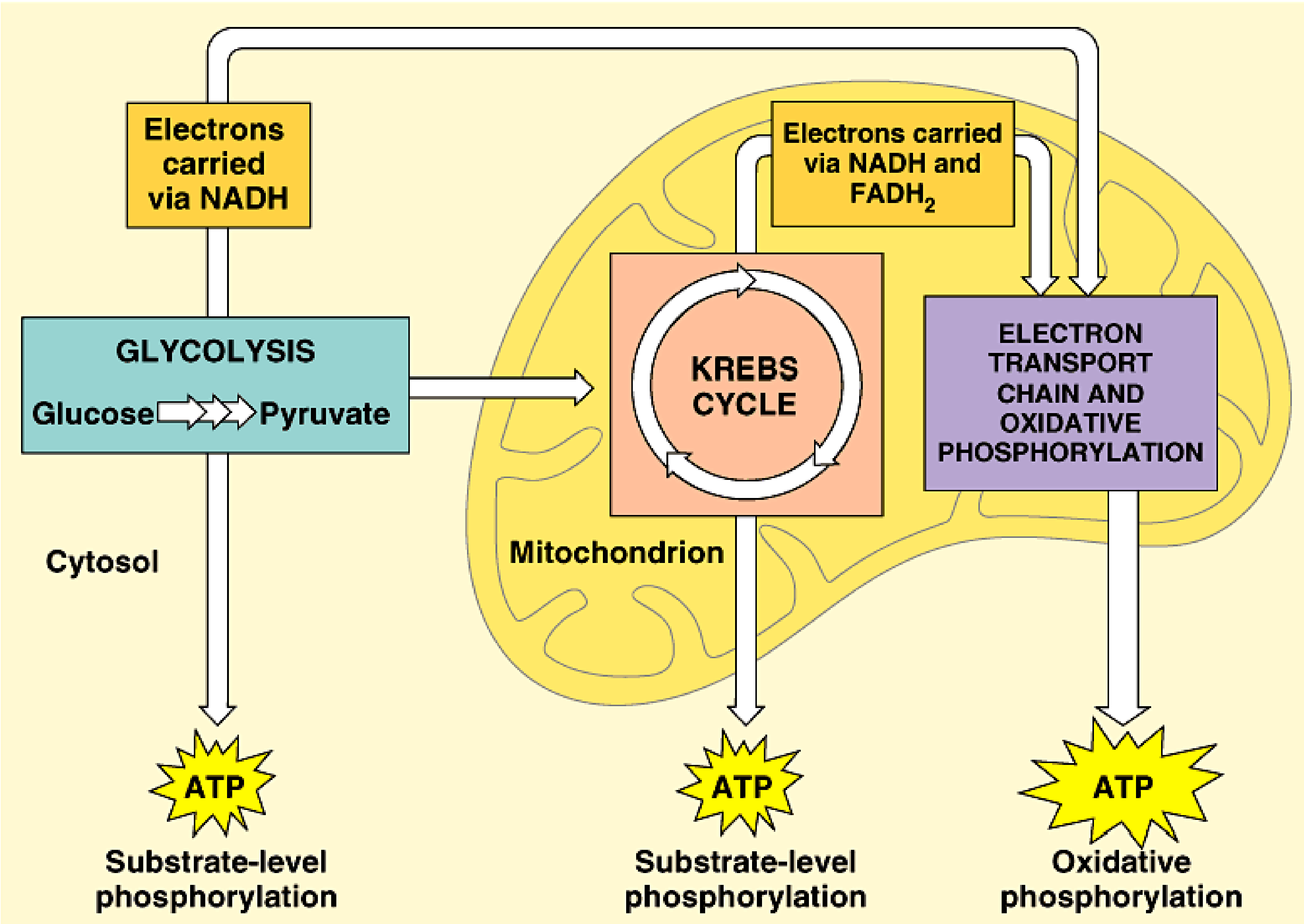
EXPERIMENT 2

Question: What is the role of H^+ pumps in ATP synthesis?



Conclusion: If an H^+ gradient is created by directional pumping, a second pump, acting as an H^+ channel, is necessary for ATP synthesis.

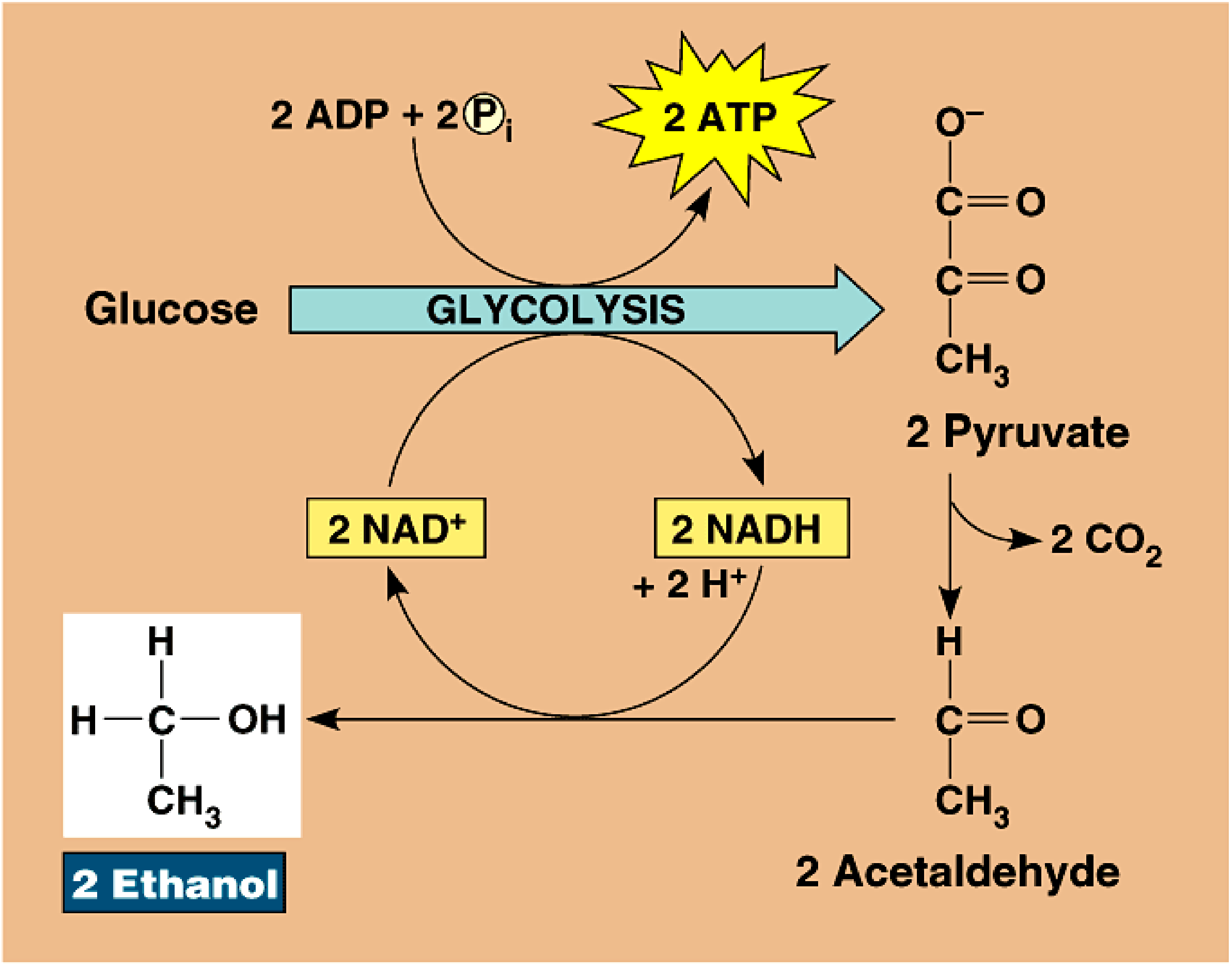
An overview of cellular respiration



I. Fermentation: ATP from Glucose, without O_2

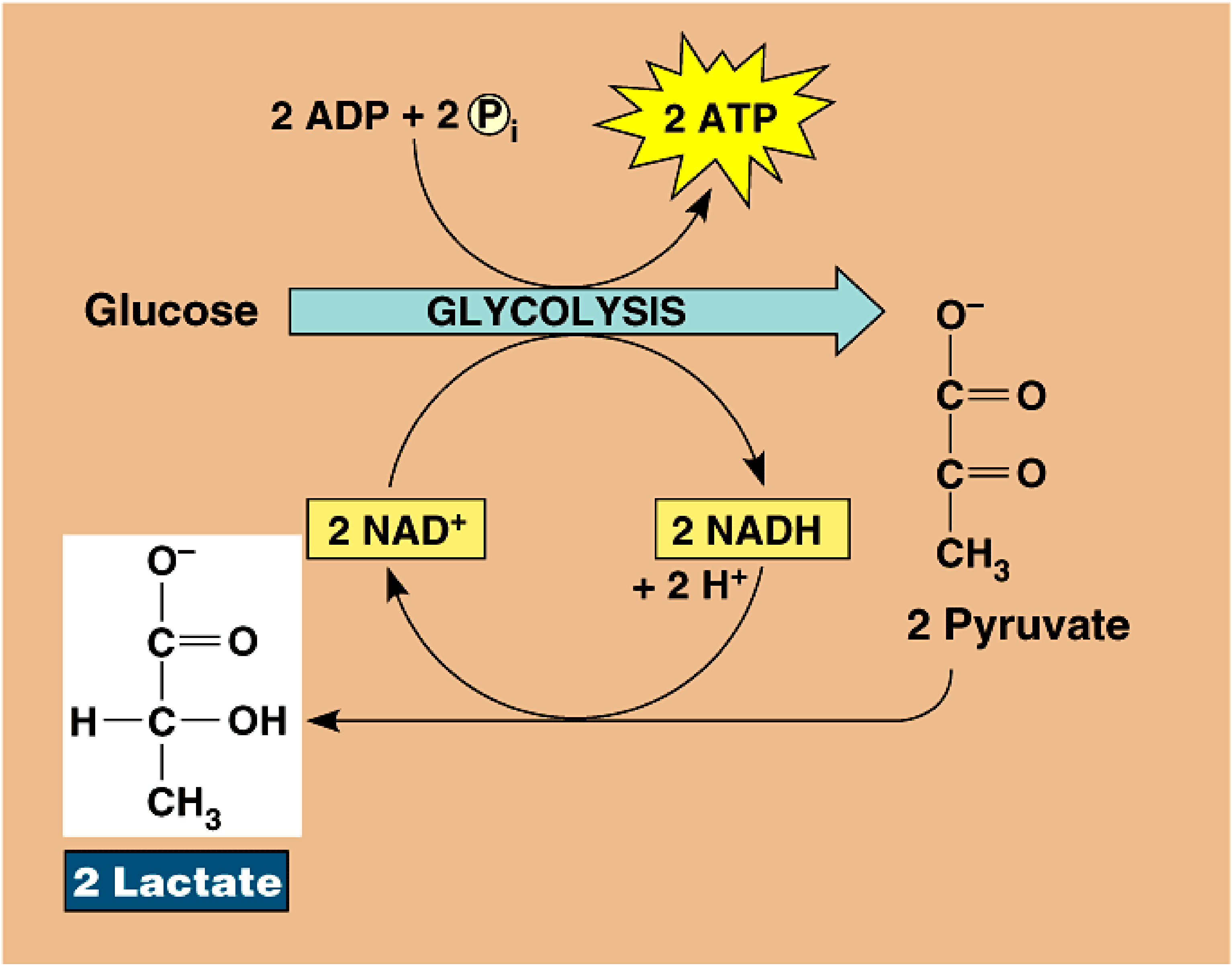
- Many organisms and some cells live without O_2, deriving energy from glycolysis and fermentation.
- Together, these pathways partly oxidize glucose and generate energy-containing products.
- Fermentation reactions anaerobically oxidize the NADH + H^+ produced in glycolysis.

Fermentation



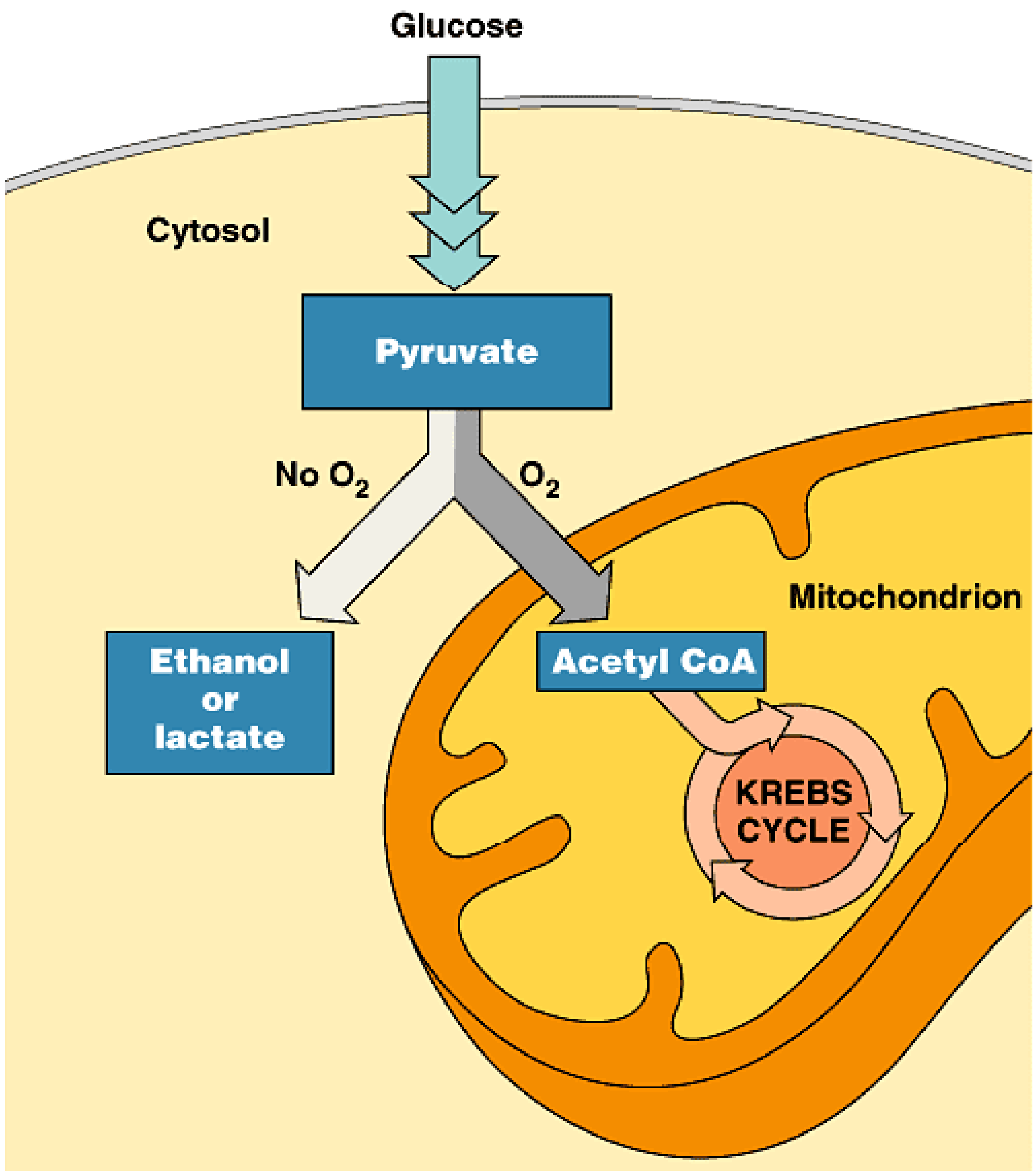
(a) Alcohol fermentation

Fermentation



(b) Lactic acid fermentation

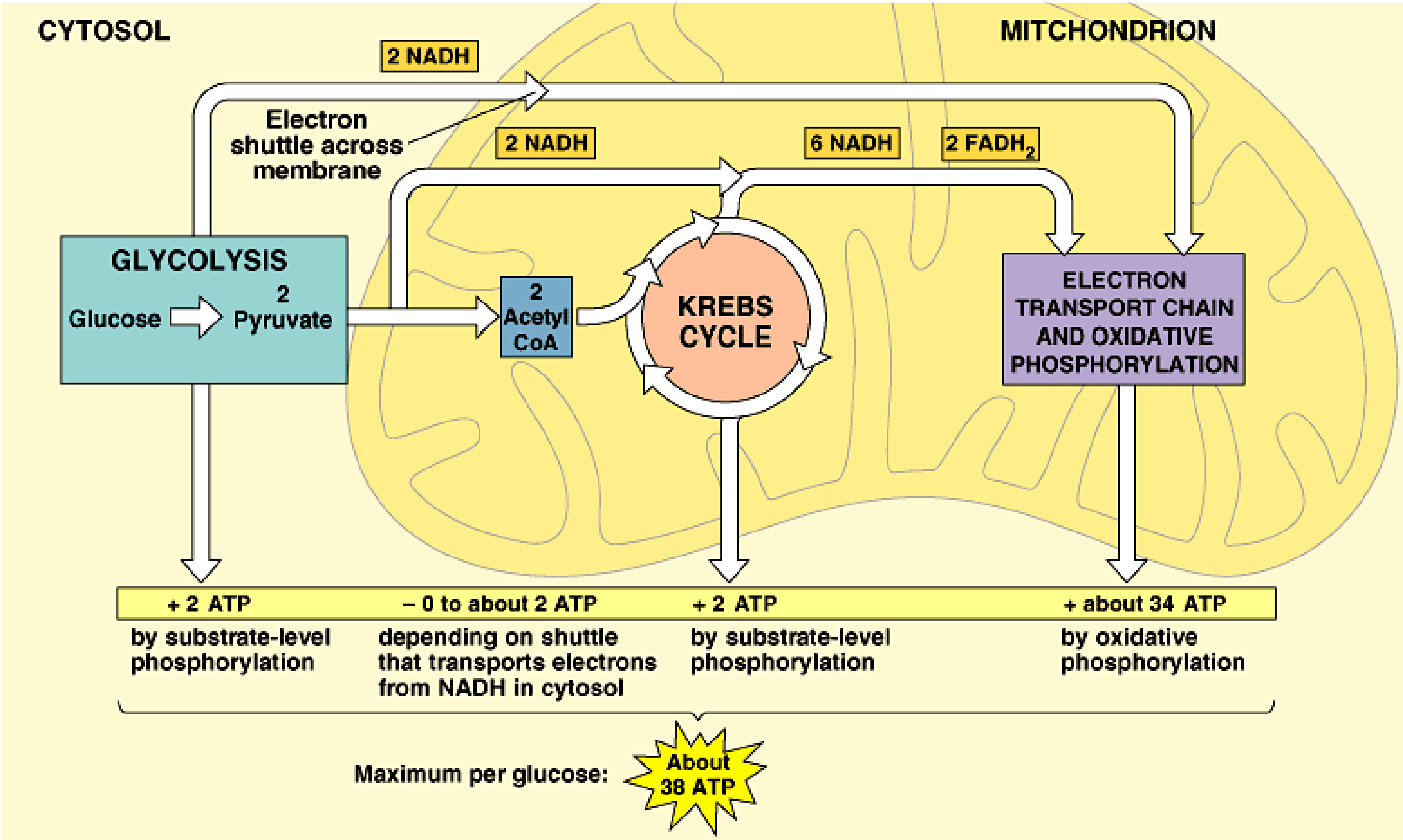
Pyruvate as a key juncture in catabolism



J. Contrasting Energy Yields

- For each molecule of glucose used, fermentation yields 2 molecules of ATP.
- In contrast, glycolysis operating with pyruvate oxidation, the citric acid cycle, and the respiratory chain yields up to 36 or 38.

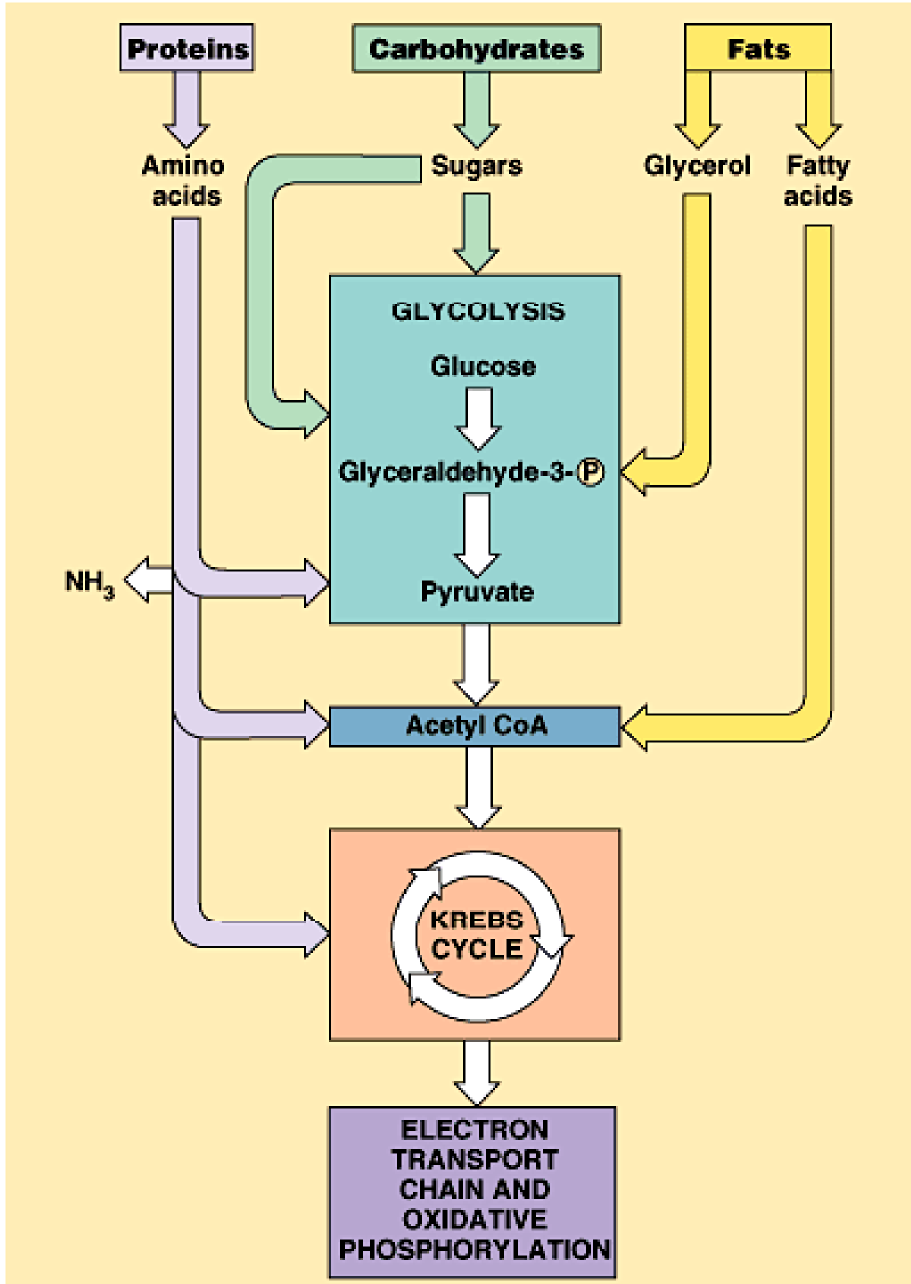
Review: How each molecule of glucose yields many ATP molecules during cellular respiration



K. Metabolic Pathways

- Catabolic pathways feed into the respiratory pathways.
- Polysaccharides are broken down into glucose, which enters glycolysis.
- Glycerol from fats also enters glycolysis, and acetyl CoA from fatty acid degradation enters the citric acid cycle.
- Proteins enter glycolysis and the citric acid cycle via amino acids.

The catabolism of various food molecules



K. Metabolic Pathways

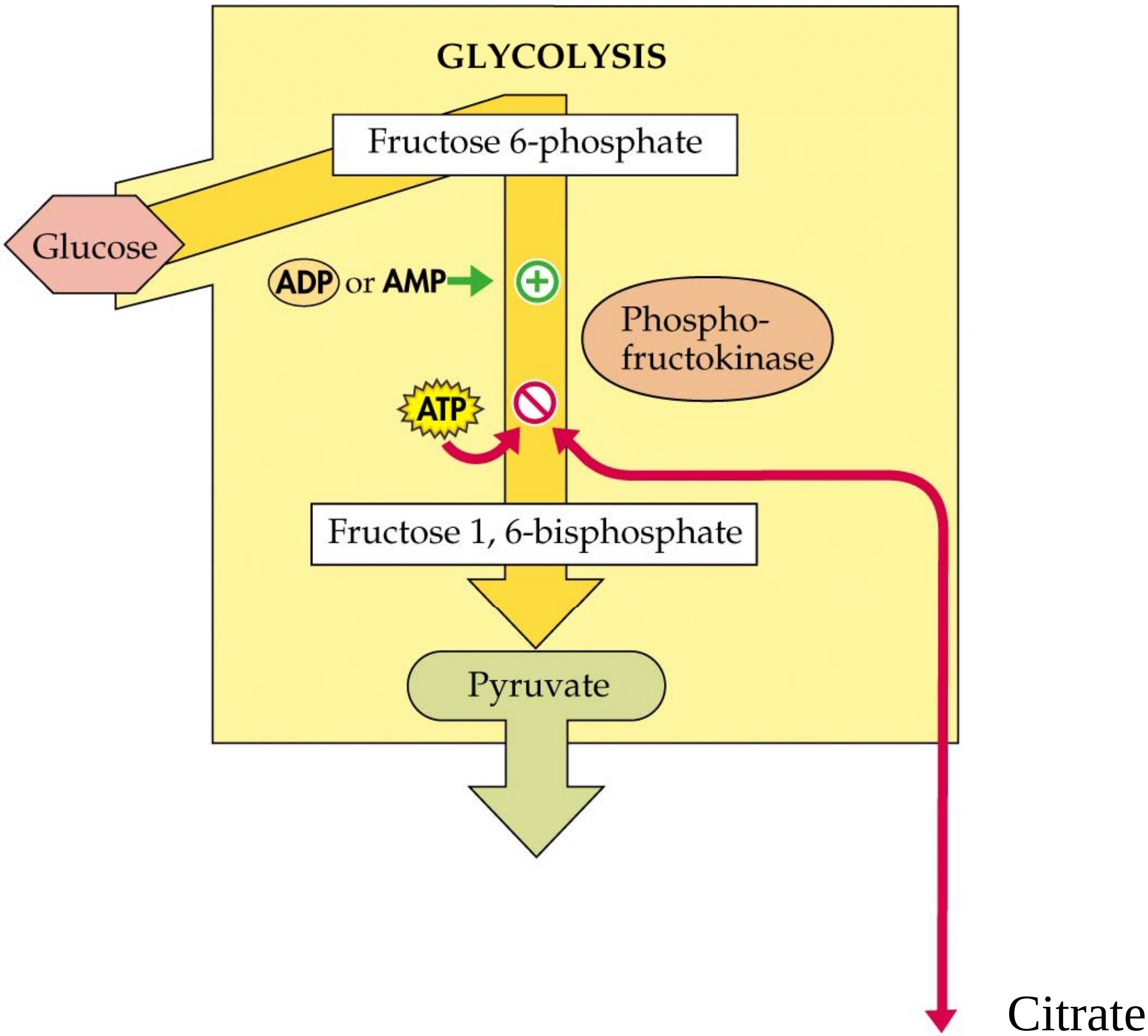
- Anabolic pathways use intermediate components of respiratory metabolism to synthesize fats, amino acids, and other essential building blocks for cellular structure and function.

L. Regulating Energy Pathways

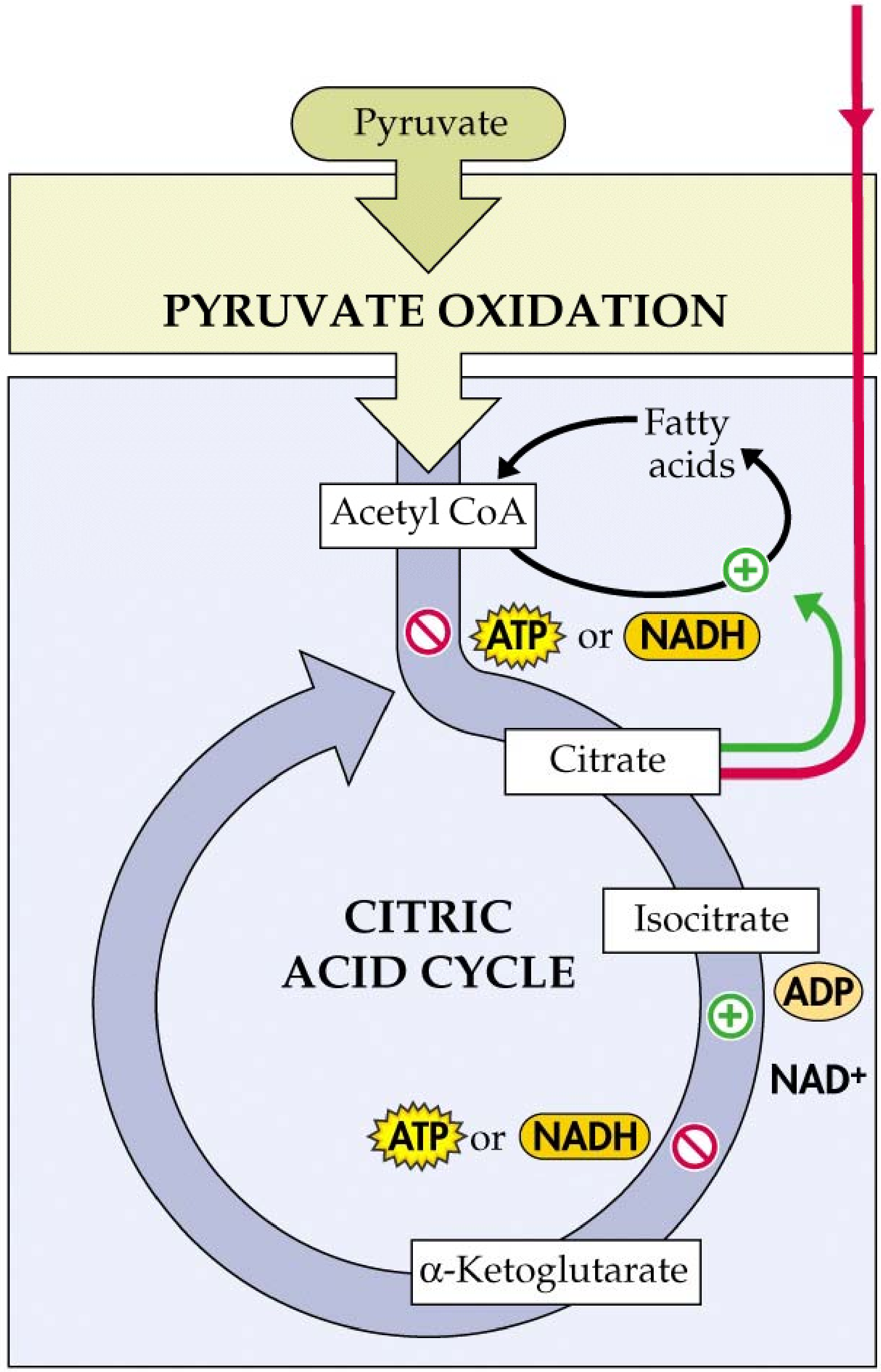
- The rates of glycolysis and the citric acid cycle are increased or decreased by the actions of ATP, ADP, NAD^+, or $NADH + H^+$ on allosteric enzymes.
- Evolution has led to metabolic efficiency.

L. Regulating Energy Pathways

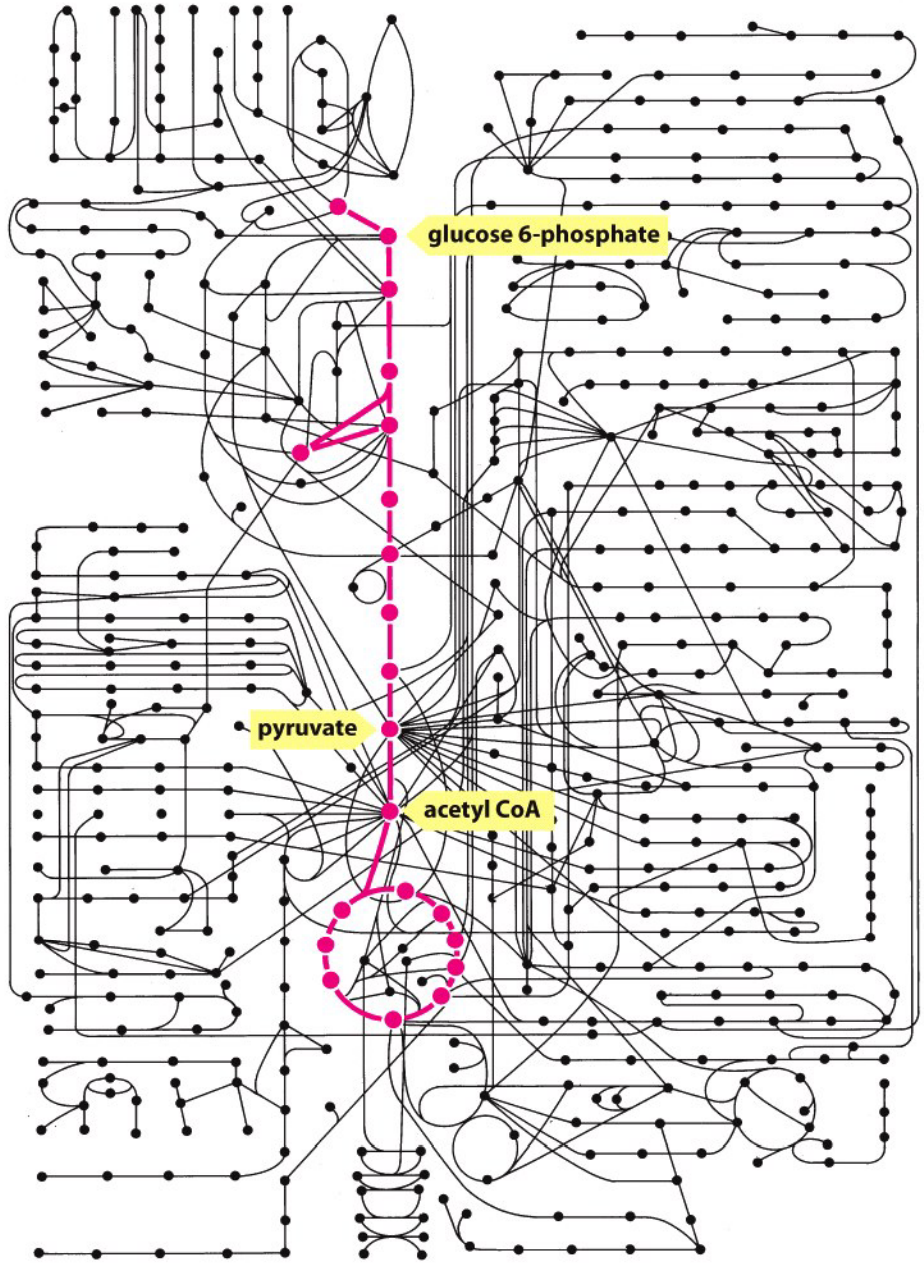
- Inhibition of the glycolytic enzyme phosphofructokinase by abundant ATP from oxidative phosphorylation slows glycolysis. ADP activates this enzyme, speeding up glycolysis.
- The citric acid cycle enzyme isocitrate dehydrogenase is inhibited by ATP and NADH and activated by ADP and NAD^+.
- Citrate also inhibits PFK.



GLYCOLYSIS
Fructose 6-phosphate
Glucose
ADP or AMP
Phospho-
fructokinase
ATP
Fructose 1, 6-bisphosphate
Pyruvate
Citrate



Isocitrate DH



glucose 6-phosphate
pyruvate
acetyl CoA