BLOQUE III:
TEMA 13.

CICLO DE KREBS, TRANSPORTE DE ELECTRONES Y FOSFORILACIÓN OXIDATIVA

ÍNDICE

- Ciclo de los ácidos tricarboxílicos
- Transporte electrónico
- Fosforilación oxidativa

Catabolismo de proteínas, grasas y glúcidos en las tres etapas de la respiración celular

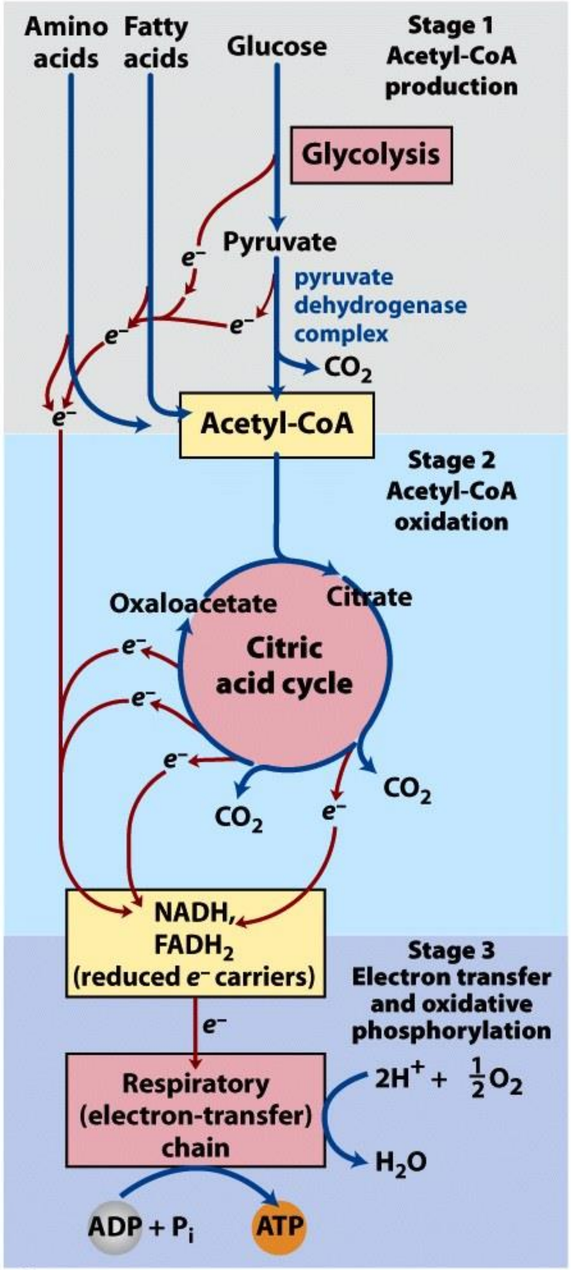
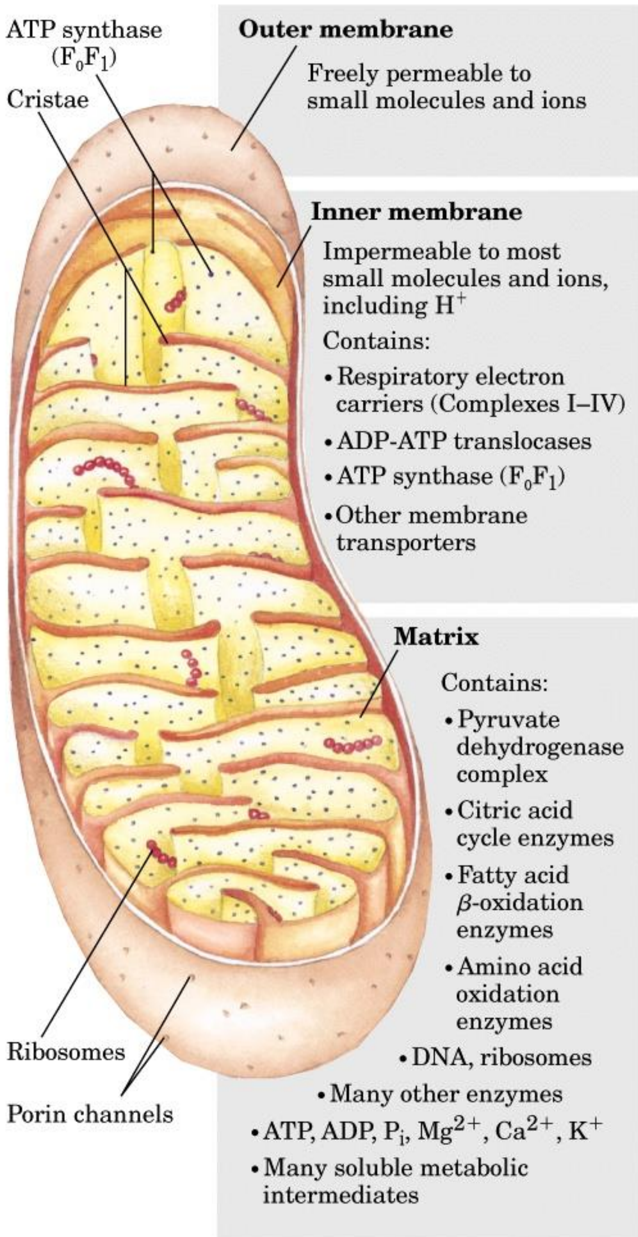
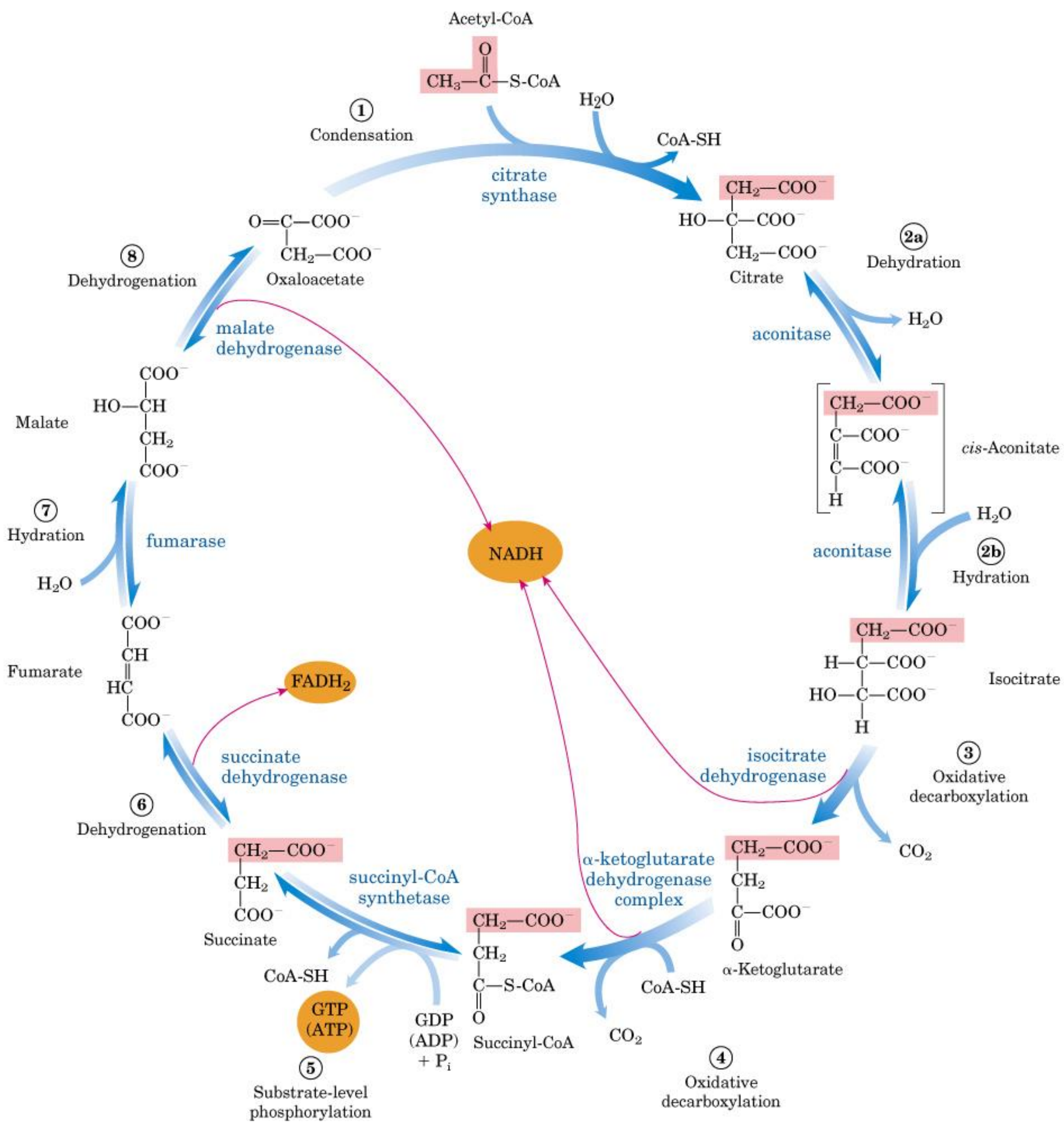


Figure 16-1
Lehninger Principles of Biochemistry, Fifth Edition

Anatomía bioquímica de una mitocondria



CICLO DEL ÁCIDO CÍTRICO (CAT)



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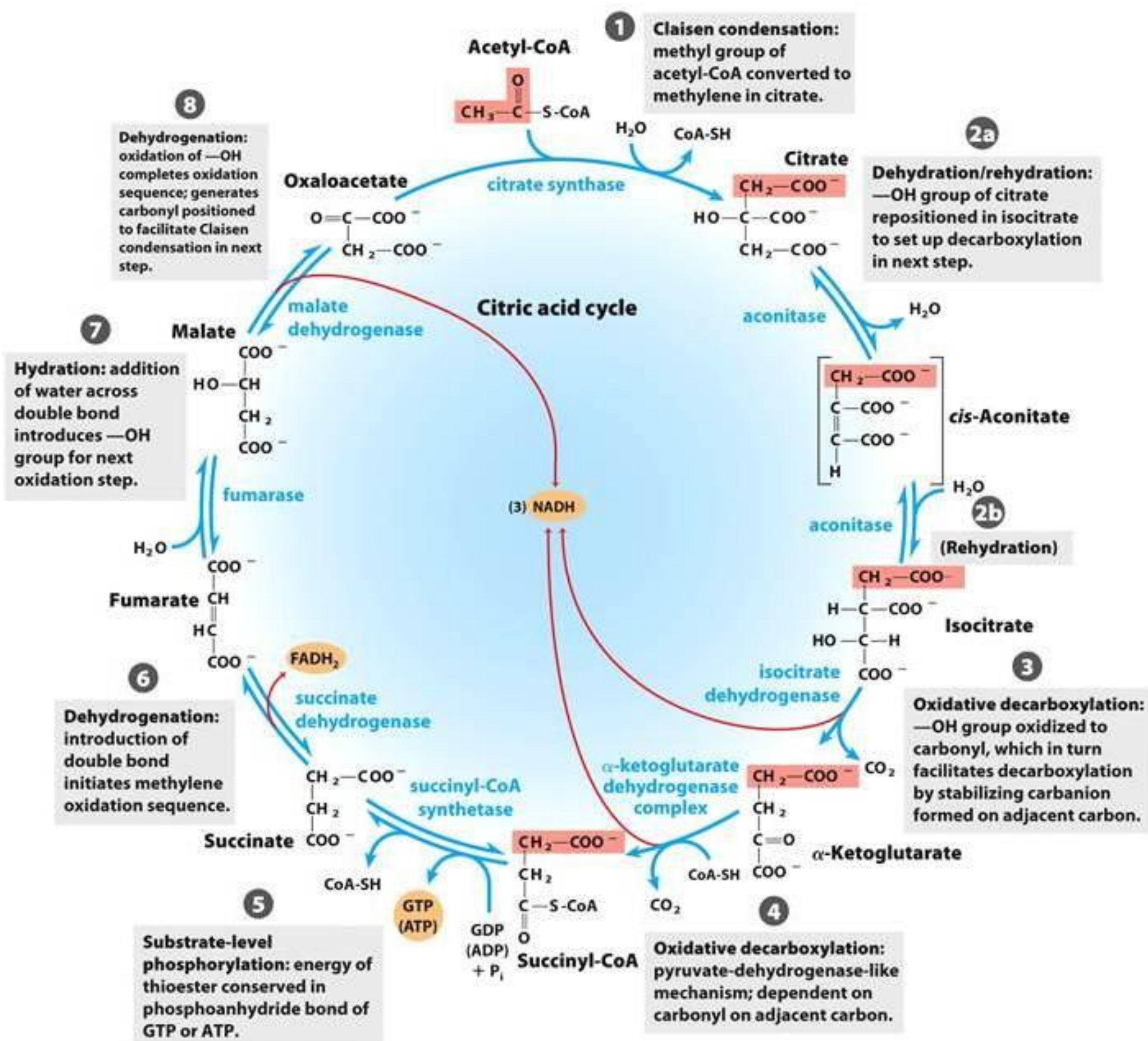

Figure 16-7
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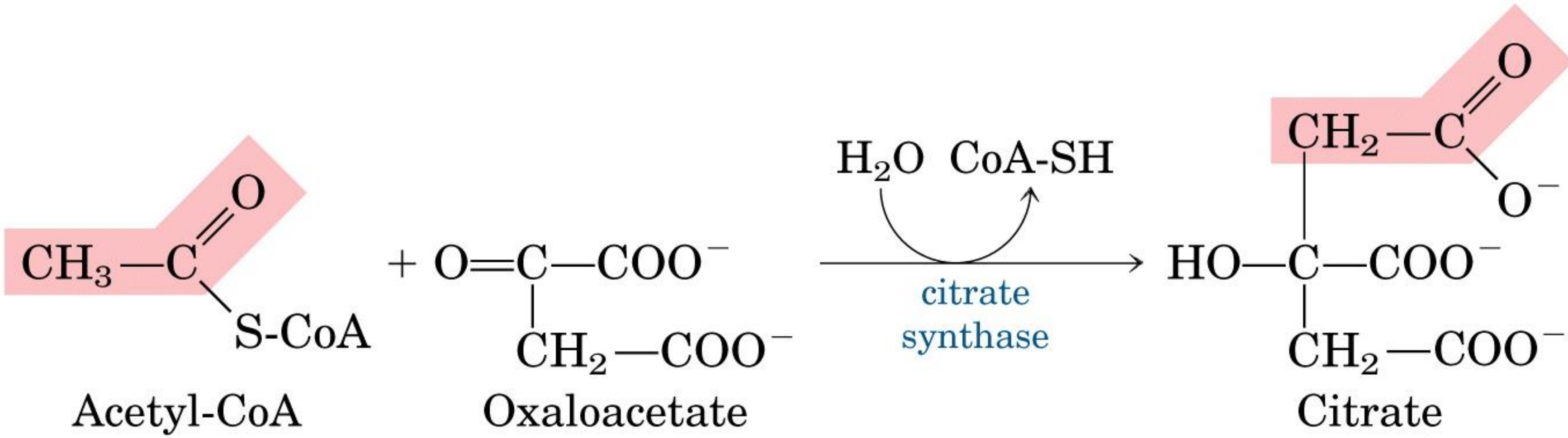
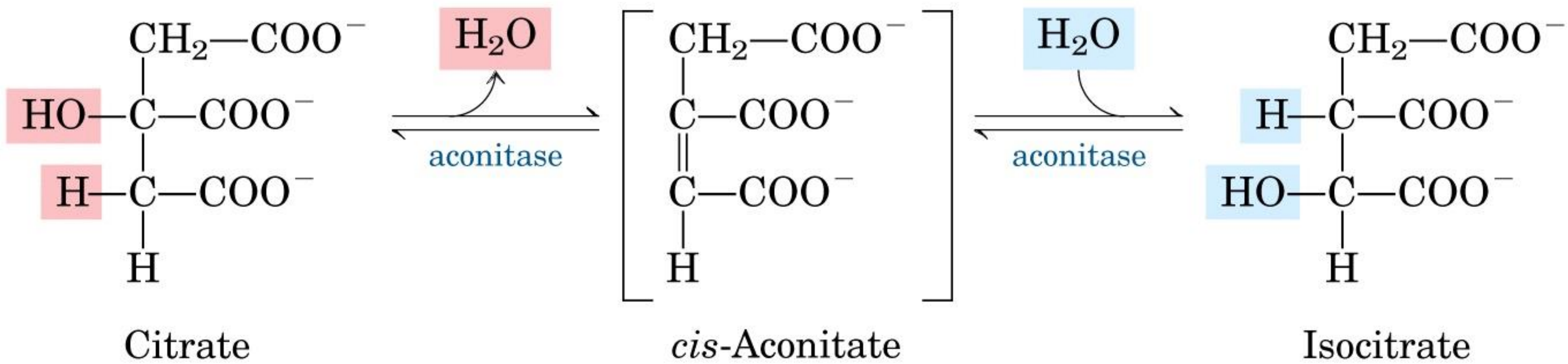
2C y 8 e^- **4C y 10 e^-** **6C y 18 e^-**

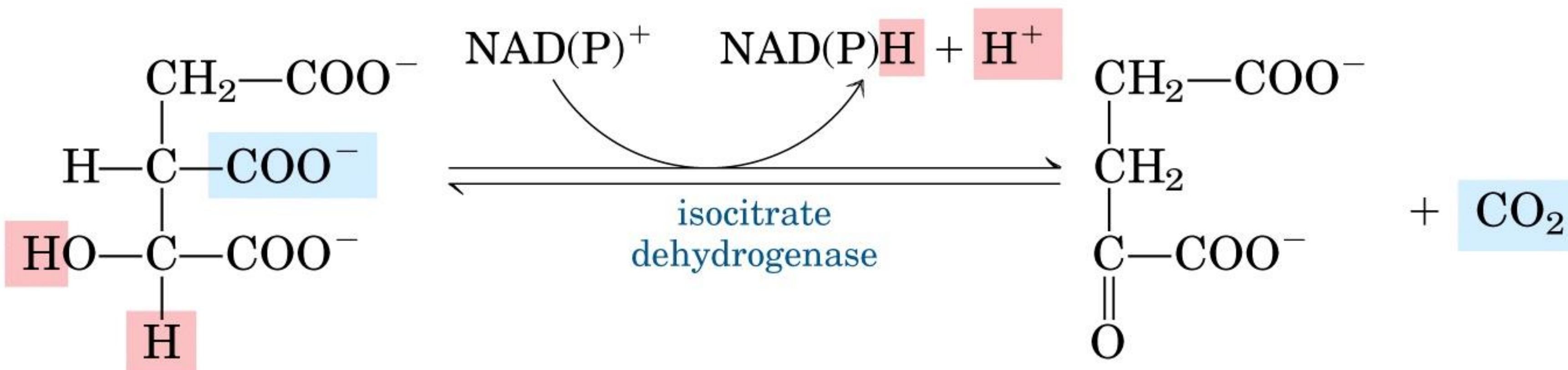


$$\Delta G'^{\circ} = -32.2 \text{ kJ/mol}$$

6C y 18 e^- **6C y 18 e^-**



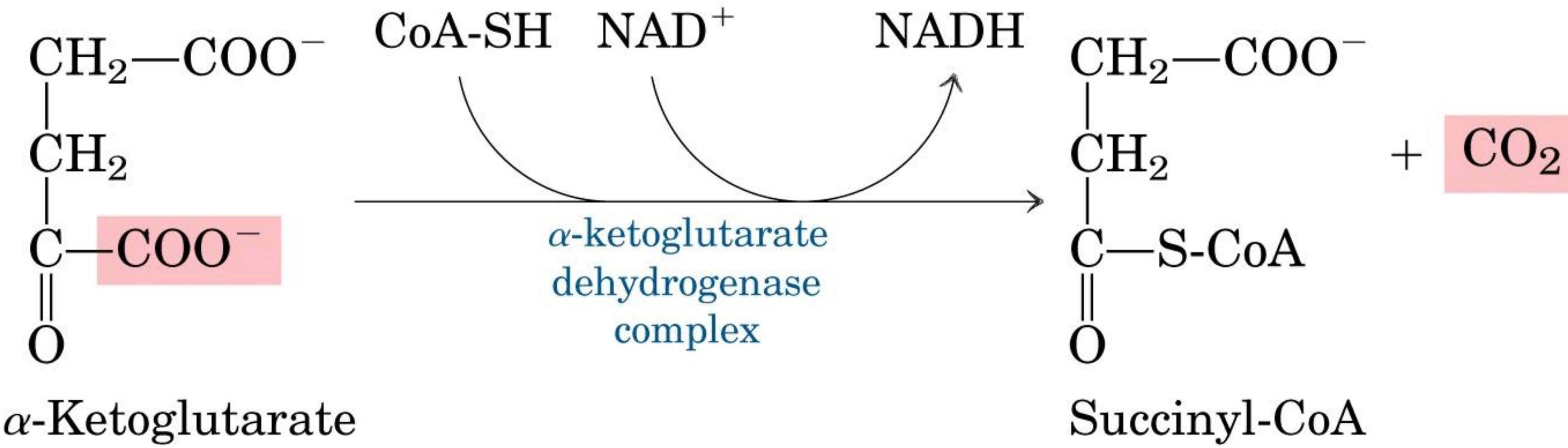
$\Delta G'^{\circ} = 13.3$ kJ/mol



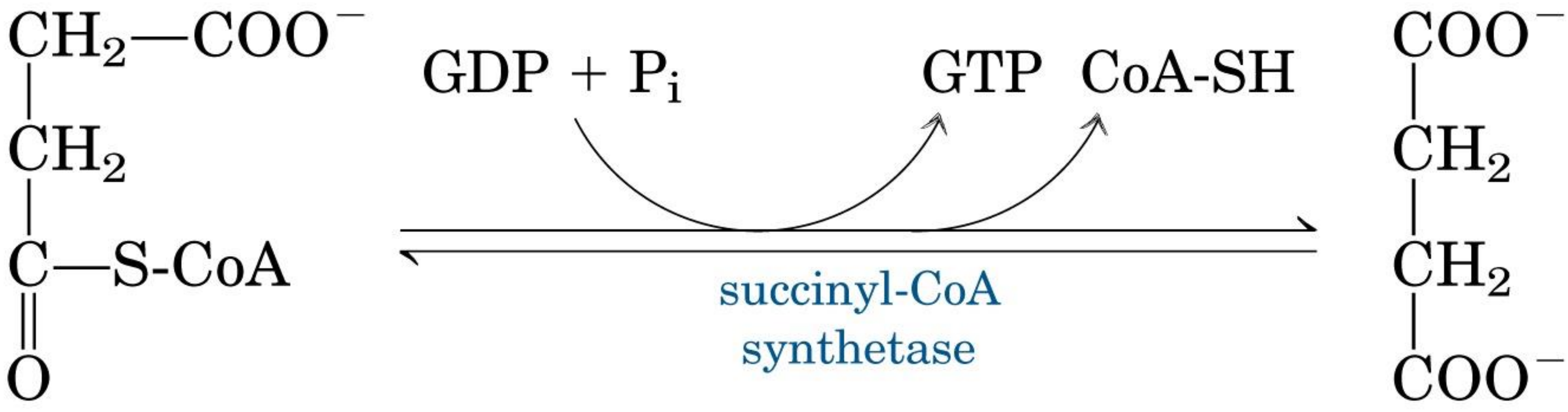
Isocitrate

α-Ketoglutarate

$$\Delta G'^{\circ} = -20.9 \text{ kJ/mol}$$



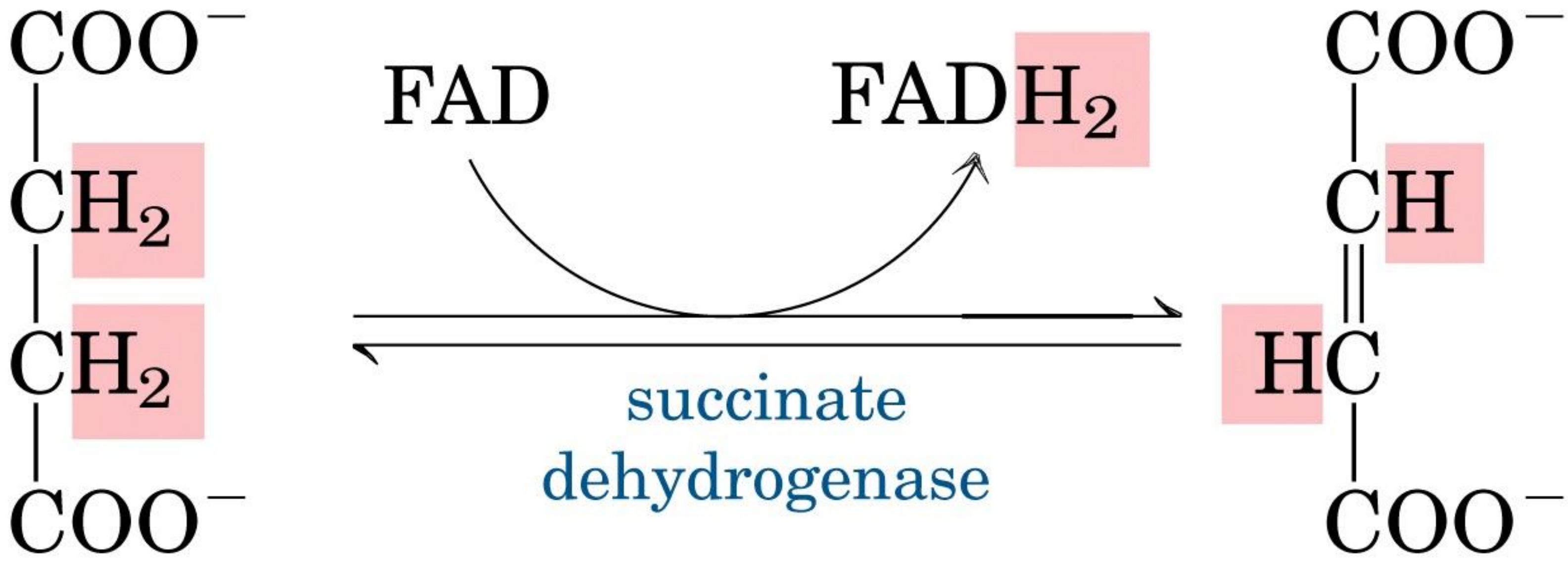
$$\Delta G'^{\circ} = -33.5 \text{ kJ/mol}$$



Succinyl-CoA

Succinate

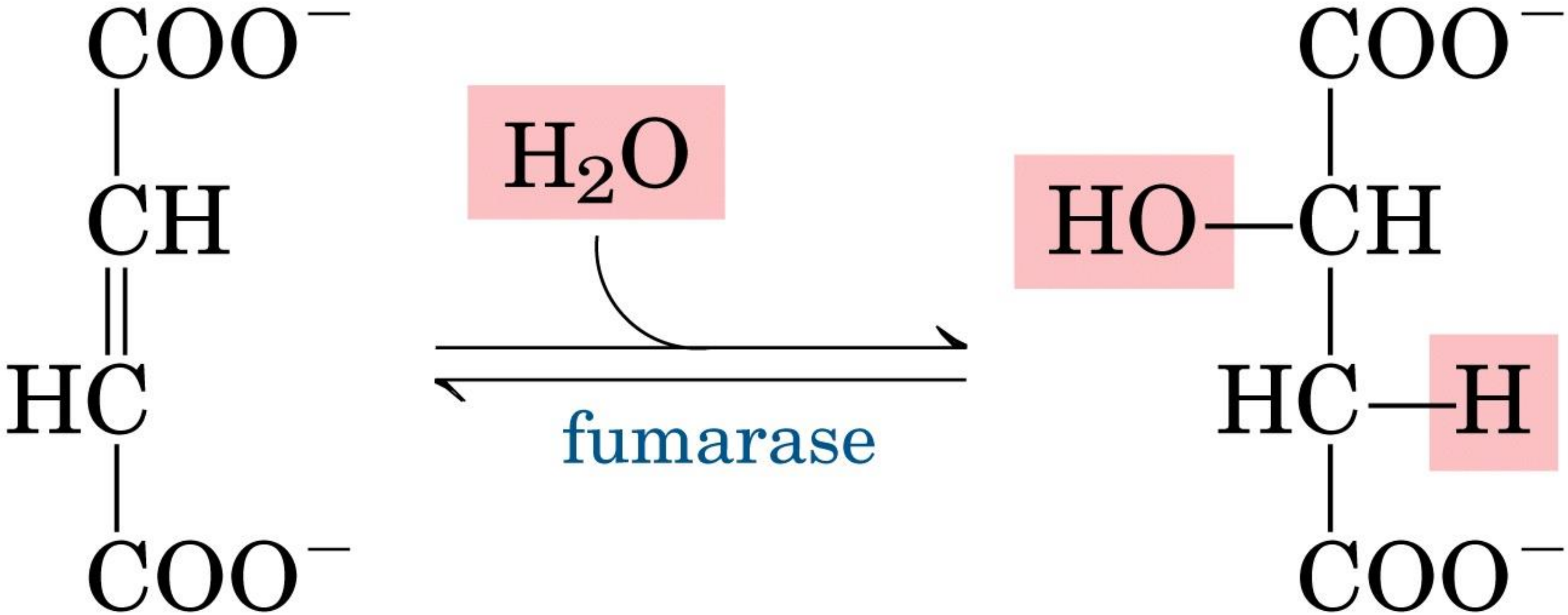
$$\Delta G'^{\circ} = -2.9 \text{ kJ/mol}$$



Succinate

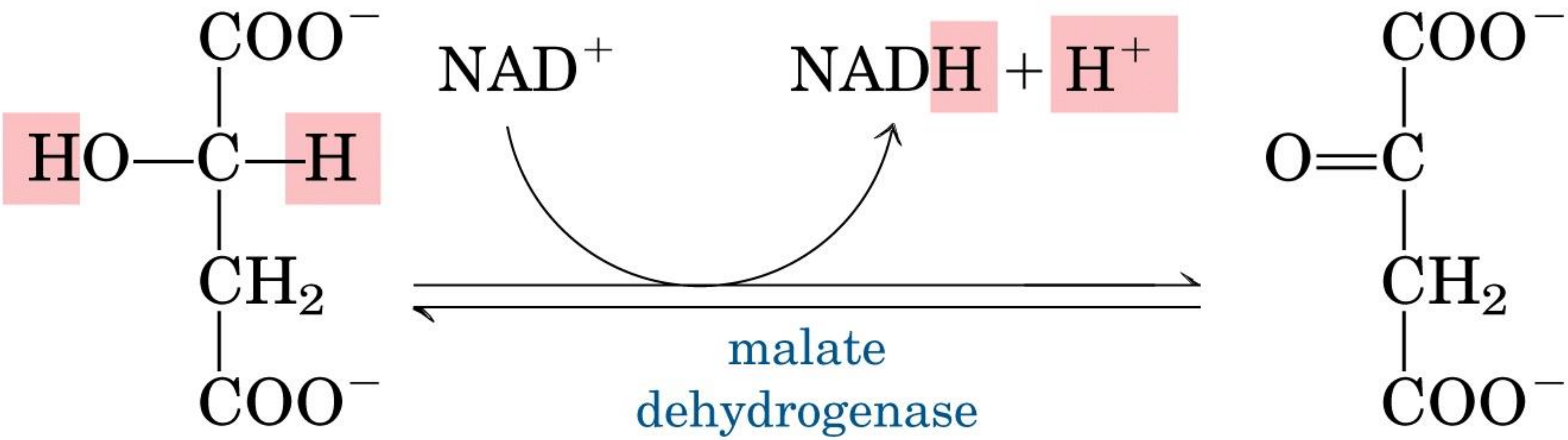
Fumarate

$$\Delta G'^{\circ} = 0 \text{ kJ/mol}$$



Fumarate L-Malate

$$\Delta G'^{\circ} = -3.8 \text{ kJ/mol}$$



L-Malate

Oxaloacetate

$$\Delta G'^{\circ} = 29.7 \text{ kJ/mol}$$

CICLO DEL ÁCIDO CÍTRICO (CAT)

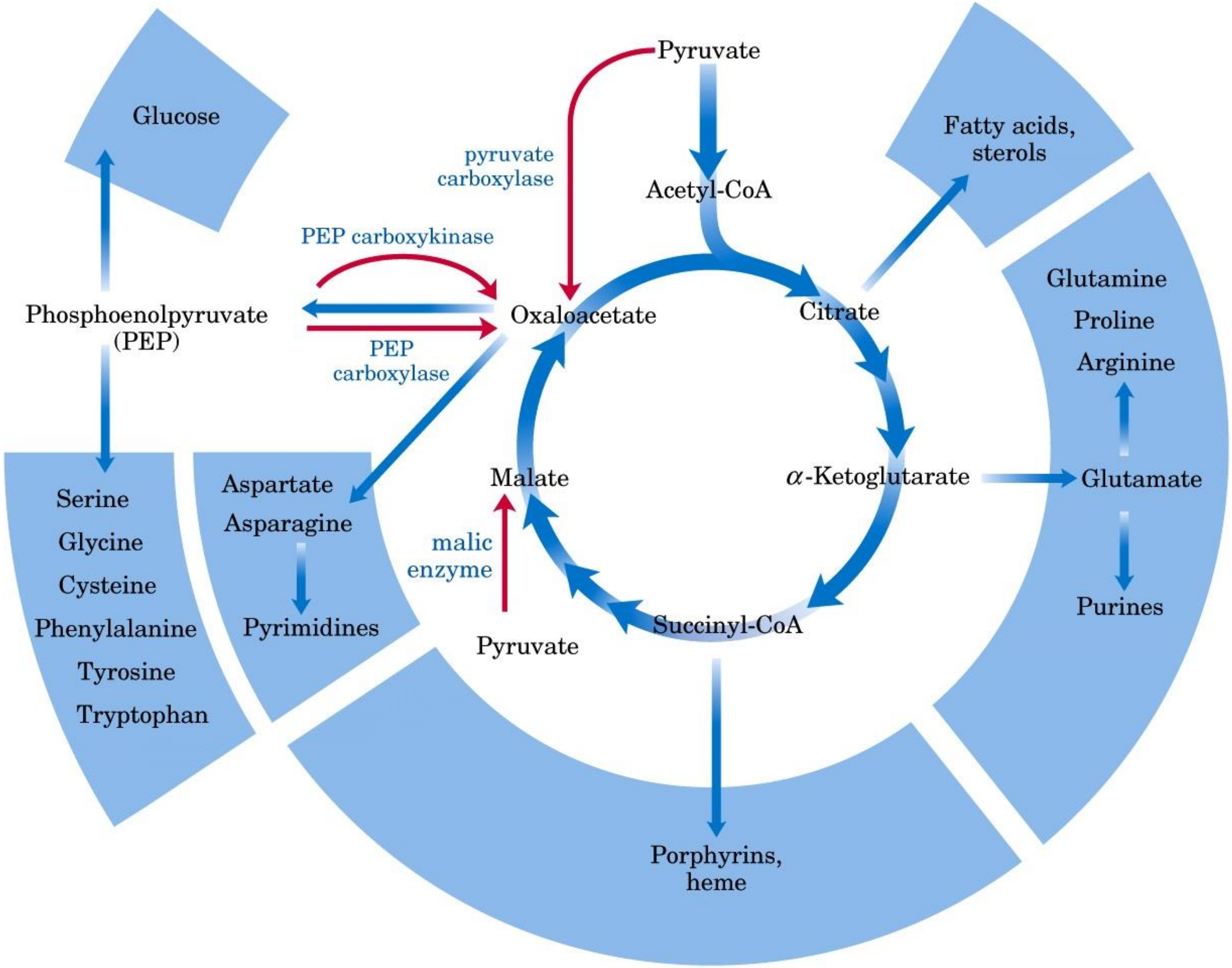
Balance completo:

Acetil CoA+ 3 NAD^++ FAD + GDP + P_i + 2 H_2O

⇩

2 CO_2+ 3 NADH + H^+ + $FADH_2$ + GTP +CoA-SH

INTERMEDIOS DEL CICLO USADOS EN ANABOLISMO



Reacciones anapleróticas

table 16–2

Anaplerotic Reactions

Reaction	Tissue(s)/organism(s)
Pyruvate + HCO_3^- + ATP $\xrightleftharpoons{\text{pyruvate carboxylase}}$ oxaloacetate + ADP + P_i	Liver, kidney
Phosphoenolpyruvate + CO_2 + GDP $\xrightleftharpoons{\text{PEP carboxykinase}}$ oxaloacetate + GTP	Heart, skeletal muscle
Phosphoenolpyruvate + HCO_3^- $\xrightleftharpoons{\text{PEP carboxylase}}$ oxaloacetate + P_i	Higher plants, yeast, bacteria
Pyruvate + HCO_3^- + NAD(P)H $\xrightleftharpoons{\text{malic enzyme}}$ malate + $NAD(P)^+$	Widely distributed in eukaryotes and prokaryotes

REGULACIÓN DEL FLUJO DE METABOLITOS

[ATP]/[ADP]

[NADH]/[NAD^+]

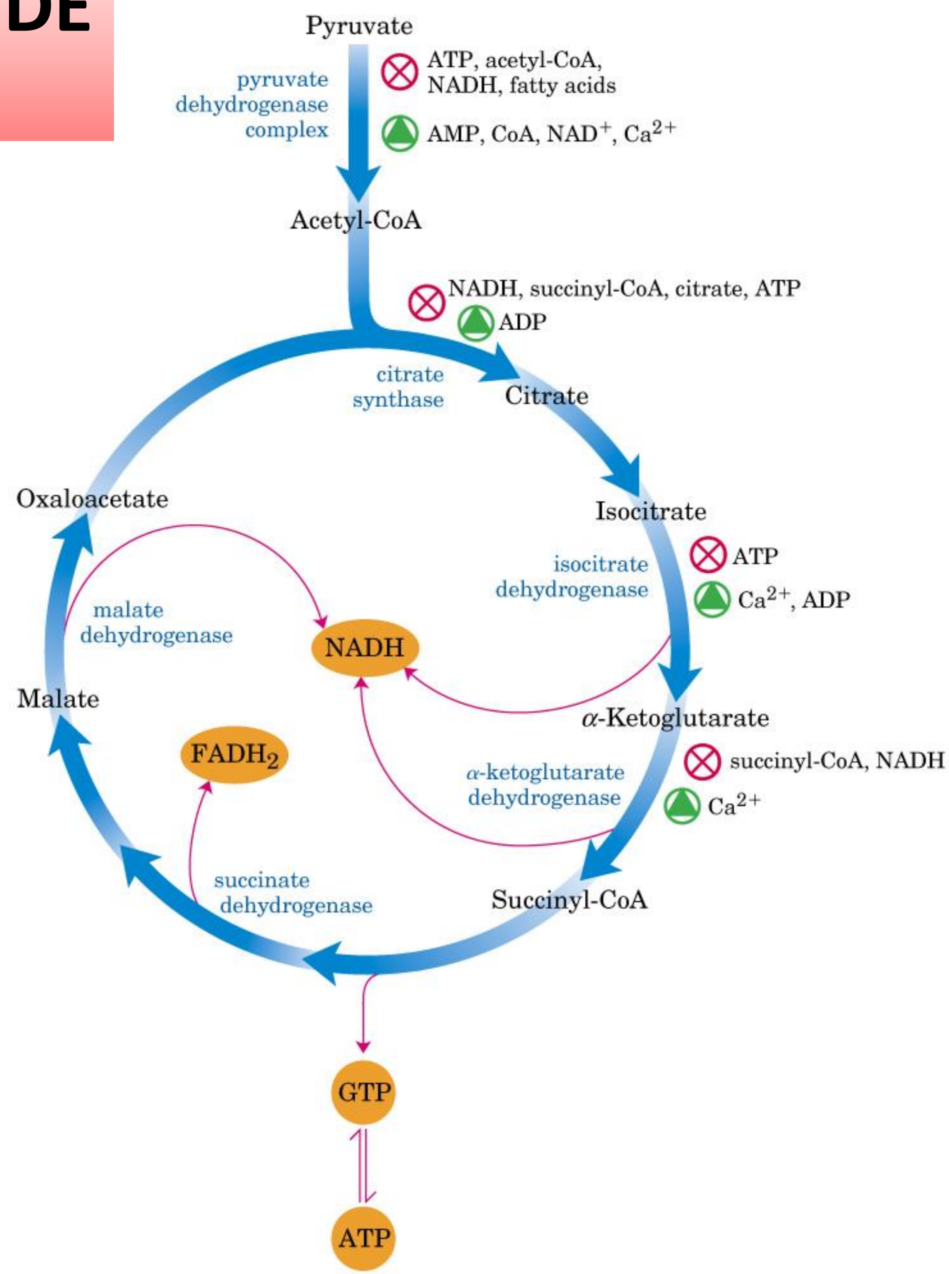


table 19–1

Some Important Reactions Catalyzed by NAD(P)H-Linked Dehydrogenases

Reaction*	Location†
NAD-linked	
α-Ketoglutarate + CoA + $NAD^+ \rightleftharpoons$ succinyl-CoA + CO_2 + NADH + H^+	M
L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	M and C
Pyruvate + CoA + $NAD^+ \rightleftharpoons$ acetyl-CoA + CO_2 + NADH + H^+	M
Glyceraldehyde 3-phosphate + P_i + $NAD^+ \rightleftharpoons$ 1,3-bisphosphoglycerate + NADH + H^+	C
Lactate + $NAD^+ \rightleftharpoons$ pyruvate + NADH + H^+	C
β-Hydroxyacyl-CoA + $NAD^+ \rightleftharpoons$ β-ketoacyl-CoA + NADH + H^+	M
NADP-linked	
Glucose 6-phosphate + $NADP^+ \rightleftharpoons$ 6-phosphogluconate + NADPH + H^+	C
NAD- or NADP-linked	
L-Glutamate + H_2O + $NAD(P)^+ \rightleftharpoons$ α-ketoglutarate + NH_4^+ + NAD(P)H	M
Isocitrate + $NAD(P)^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NAD(P)H + H^+	M and C

*These reactions and their enzymes are discussed in Chapters 15 through 18.

†M designates mitochondria; C, cytosol.

Tipos de transferencia electrónica

(1) Transferencia directa de electrones

(2) Transferencia de un átomo de hidrógeno

(3) Transferencia de un ión hidruro

Transportadores de electrones

Nucleótidos de nicotinamida:

NAD^+, $NADP^+$

Nucleótidos de flavina:

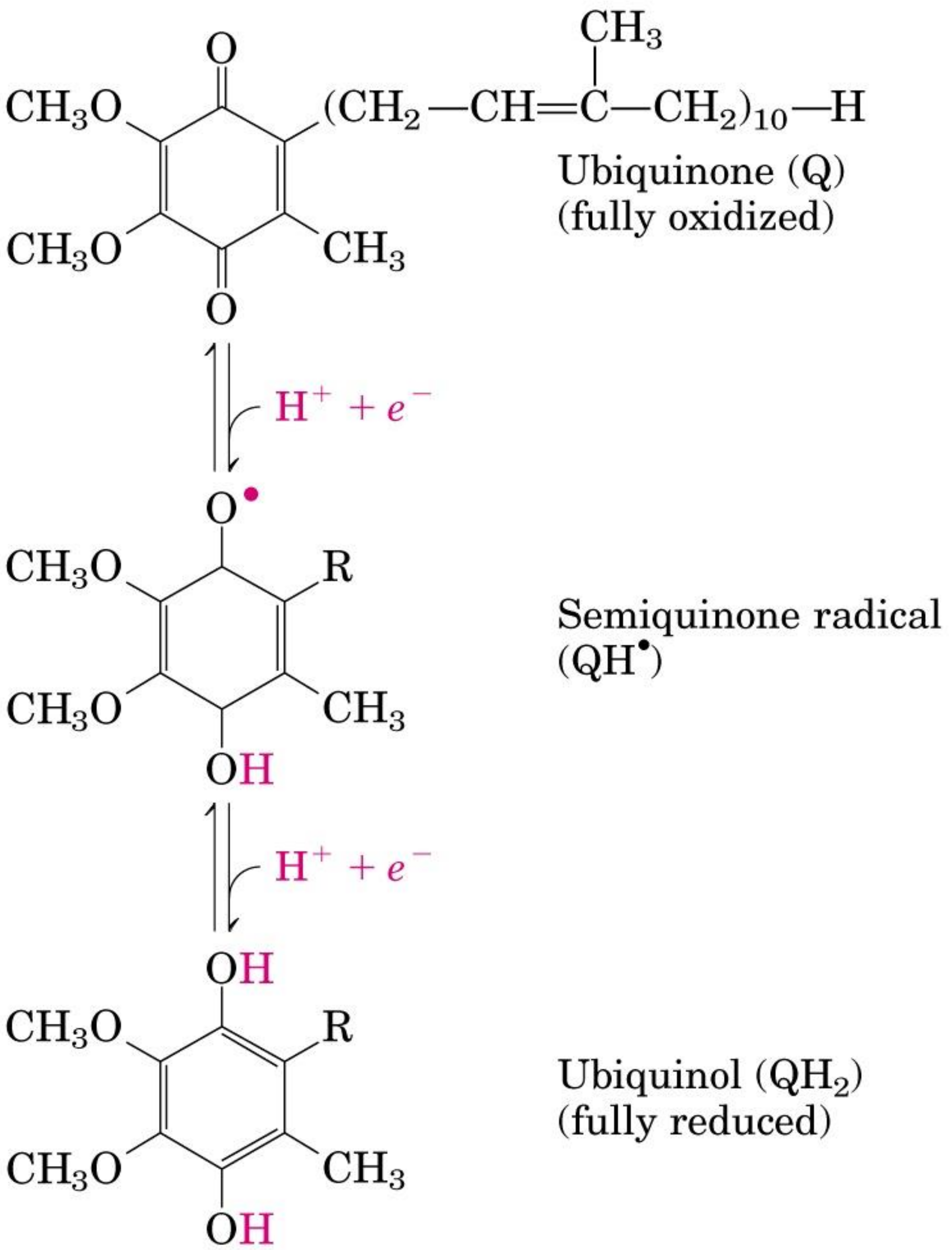
FMN, FAD

UBIOQUINONA

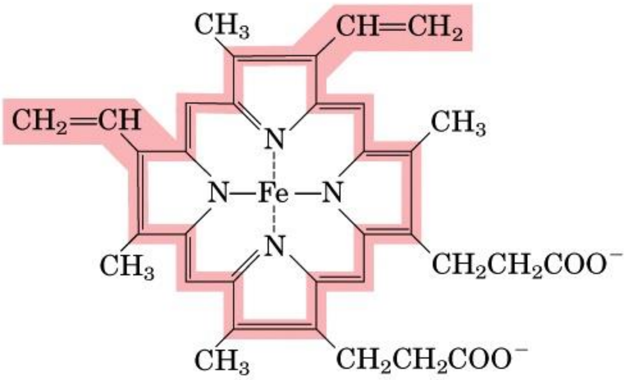
CITOCROMOS

Proteínas con centros hierro-azufre

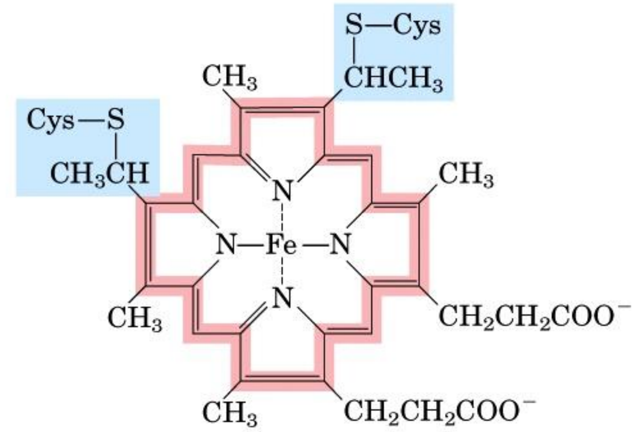
UBIOQUINONA



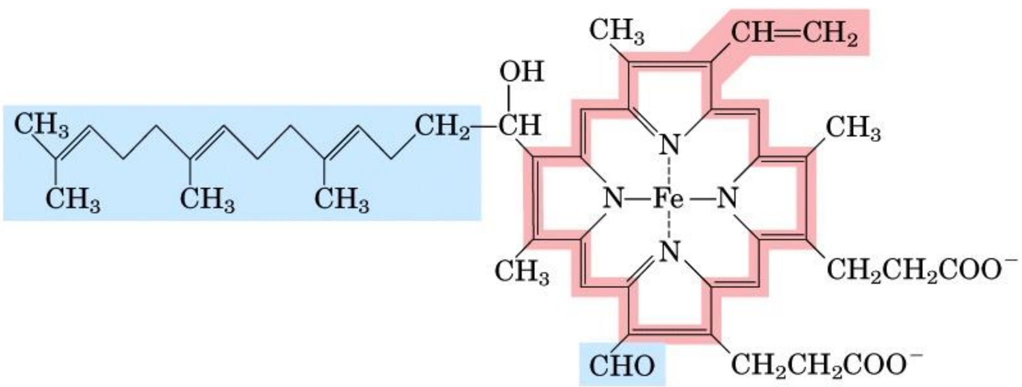
GRUPOS PROSTÉTICOS DE CITOCROMOS



Iron protoporphyrin IX
(in *b*-type cytochromes)



Heme C
(in *c*-type cytochromes)



Heme A
(in *a*-type cytochromes)

table 19–2

Standard Reduction Potentials of Respiratory Chain and Related Electron Carriers

Redox reaction (half-reaction)	**E'° (V)**
$2H^+ + 2e^- \longrightarrow H_2$	−0.414
$NAD^+ + H^+ + 2e^- \longrightarrow NADH$	−0.320
$NADP^+ + H^+ + 2e^- \longrightarrow NADPH$	−0.324
NADH dehydrogenase (FMN) $+ 2H^+ + 2e^- \longrightarrow$ NADH dehydrogenase ($FMNH_2$)	−0.30
Ubiquinone $+ 2H^+ + 2e^- \longrightarrow$ ubiquinol	0.045
Cytochrome *b* (Fe^{3+}) $+ e^- \longrightarrow$ cytochrome *b* (Fe^{2+})	0.077
Cytochrome c_1 (Fe^{3+}) $+ e^- \longrightarrow$ cytochrome c_1 (Fe^{2+})	0.22
Cytochrome *c* (Fe^{3+}) $+ e^- \longrightarrow$ cytochrome *c* (Fe^{2+})	0.254
Cytochrome *a* (Fe^{3+}) $+ e^- \longrightarrow$ cytochrome *a* (Fe^{2+})	0.29
Cytochrome a_3 (Fe^{3+}) $+ e^- \longrightarrow$ cytochrome a_3 (Fe^{2+})	0.55
$\frac{1}{2}O_2 + 2H^+ + 2e^- \longrightarrow H_2O$	0.816

Método para determinar la secuencia de transportadores electrónicos

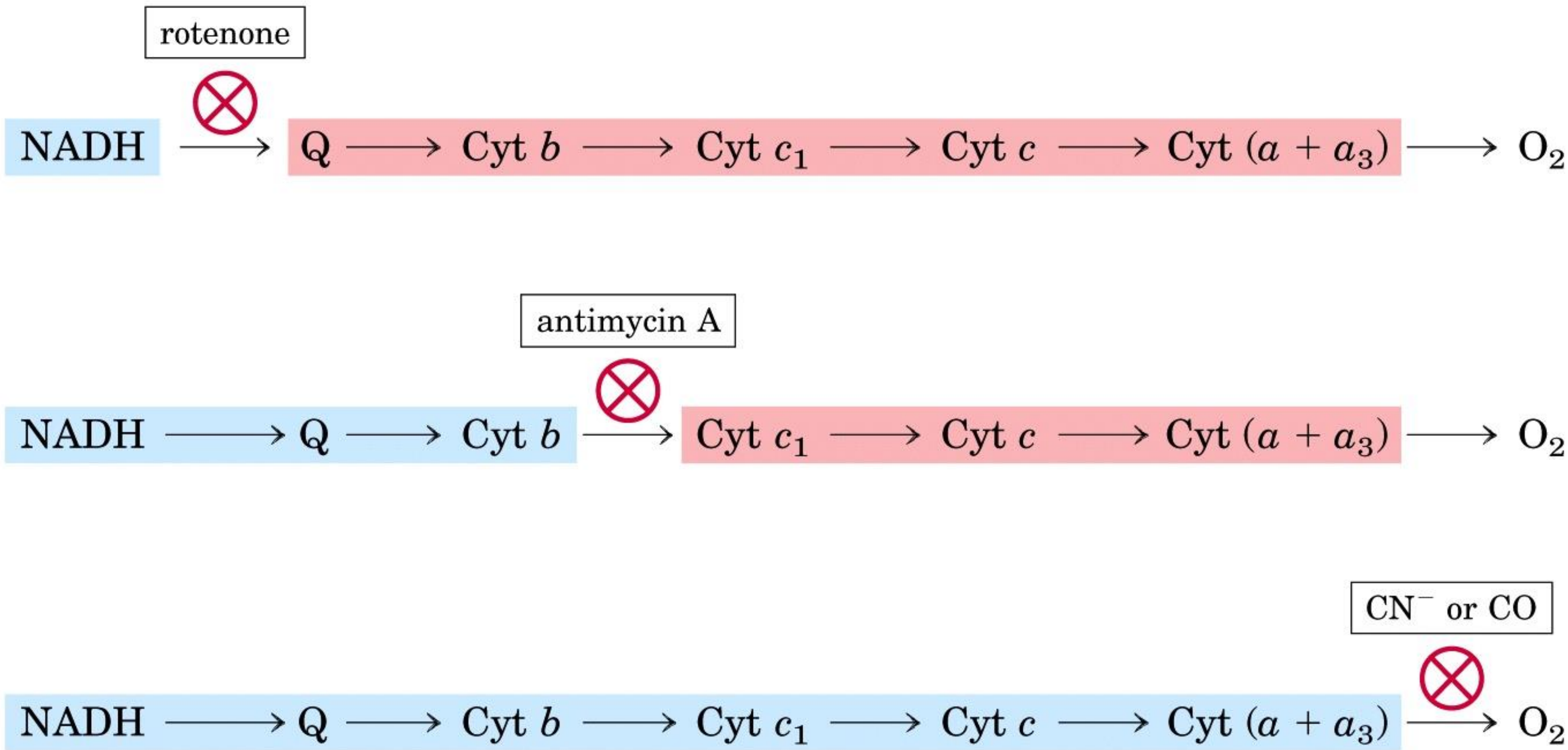


table 19–4

Some Agents That Interfere with Oxidative Phosphorylation or Photophosphorylation

Type of interference	Compound*	Target/mode of action
Inhibition of electron transfer	Cyanide Carbon monoxide	Inhibit cytochrome oxidase
	Antimycin A	Blocks electron transfer from cytochrome *b* to cytochrome c_1
	Myxothiazol Rotenone Amytal Piericidin A	Prevent electron transfer from Fe-S center to ubiquinone
	DCMU	Competes with Q_B for binding site in PSII
Inhibition of ATP synthase	Aurovertin	Inhibits F_1
	Oligomycin Venturicidin	Inhibit F_o and CF_o
	DCCD	Blocks proton flow through F_o and CF_o
Uncoupling of phosphorylation from electron transfer	FCCP DNP	Hydrophobic proton carriers
	Valinomycin	K^+ ionophore
	Thermogenin	Forms proton-conducting pores in inner membrane of brown fat mitochondria
Inhibition of ATP-ADP exchange	Atractyloside	Inhibits adenine nucleotide translocase

*DCMU is 3-(3,4-dichlorophenyl)-1,1-dimethylurea; DCCD, dicyclohexylcarbodiimide; FCCP, cyanide-*p*-trifluoromethoxyphenylhydrazone; DNP, 2,4-dinitrophenol.

CADENA DE TRANSPORTE ELECTRÓNICO

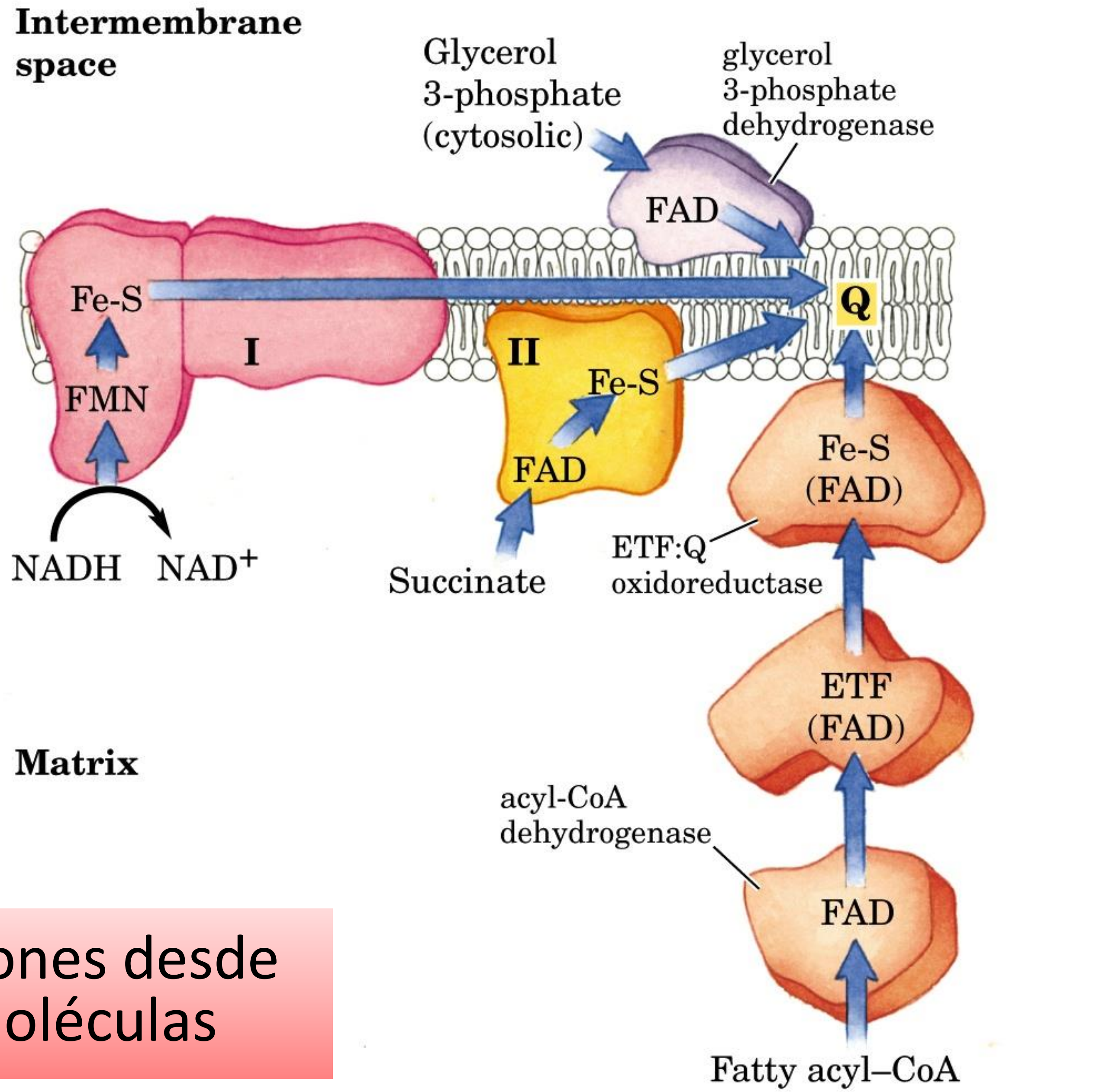
table 19–3

Protein Components of the Mitochondrial Electron-Transfer Chain

Enzyme complex	Mass (kDa)	Number of subunits*	Prosthetic group(s)
I NADH dehydrogenase	850	42 (14)	FMN, Fe-S
II Succinate dehydrogenase	140	5	FAD, Fe-S
III Ubiquinone: cytochrome *c* oxidoreductase	250	11	Hemes, Fe-S
Cytochrome *c*†	13	1	Heme
IV Cytochrome oxidase	160	13 (3–4)	Hemes; Cu_A, Cu_B

*Numbers of subunits in the bacterial equivalents in parentheses.

†Cytochrome *c* is not part of an enzyme complex; it moves between Complexes III and IV as a freely soluble protein.



Ruta de los electrones desde diferentes biomoléculas

Complejo I: NADH deshidrogenasa

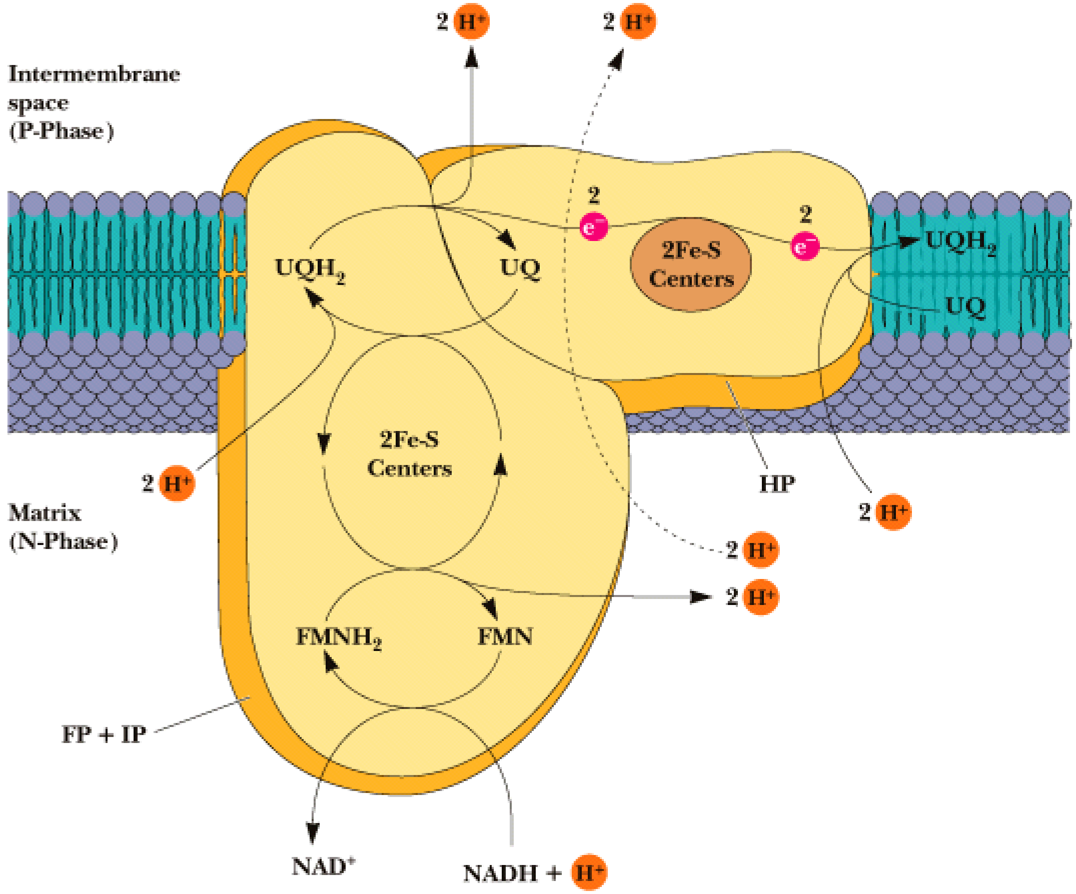
(1) Transferencia exergónica

$$NADH + H^+ + Q \rightarrow NAD^+ + QH_2$$

(2) Transferencia endergónica de 4 protones

$$NADH + 5\,H^+_N + Q \rightarrow NAD^+ + QH_2 + 4\,H^+_P$$

Garrett & Grisham: Biochemistry, 2/e
Figure 21.6



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Complejo II: Succinato deshidrogenasa

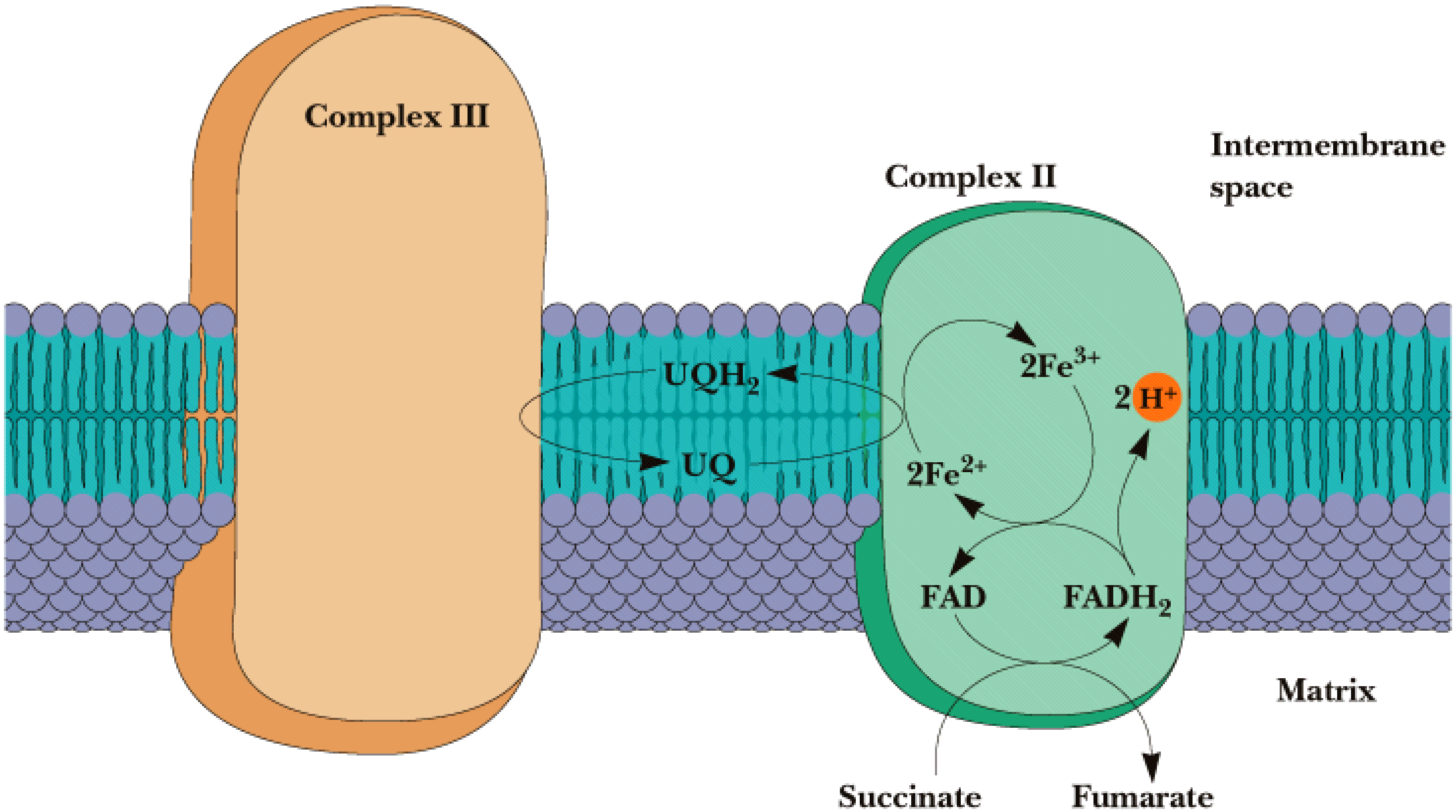
Flavoproteína; FAD unido covalentemente

2 Proteínas ferro-sulfuradas con centros 4Fe-4S, 3Fe-4S, 2Fe-2S

succinate $\rightarrow$ $FADH_2$ $\rightarrow$ $2Fe^{2+}$ $\rightarrow$ UQH_2

$$\text{succinate} + \text{UQ} \rightarrow \text{fumarate} + \text{UQH}_2$$

Garrett & Grisham: Biochemistry, 2/e
Figure 21.8



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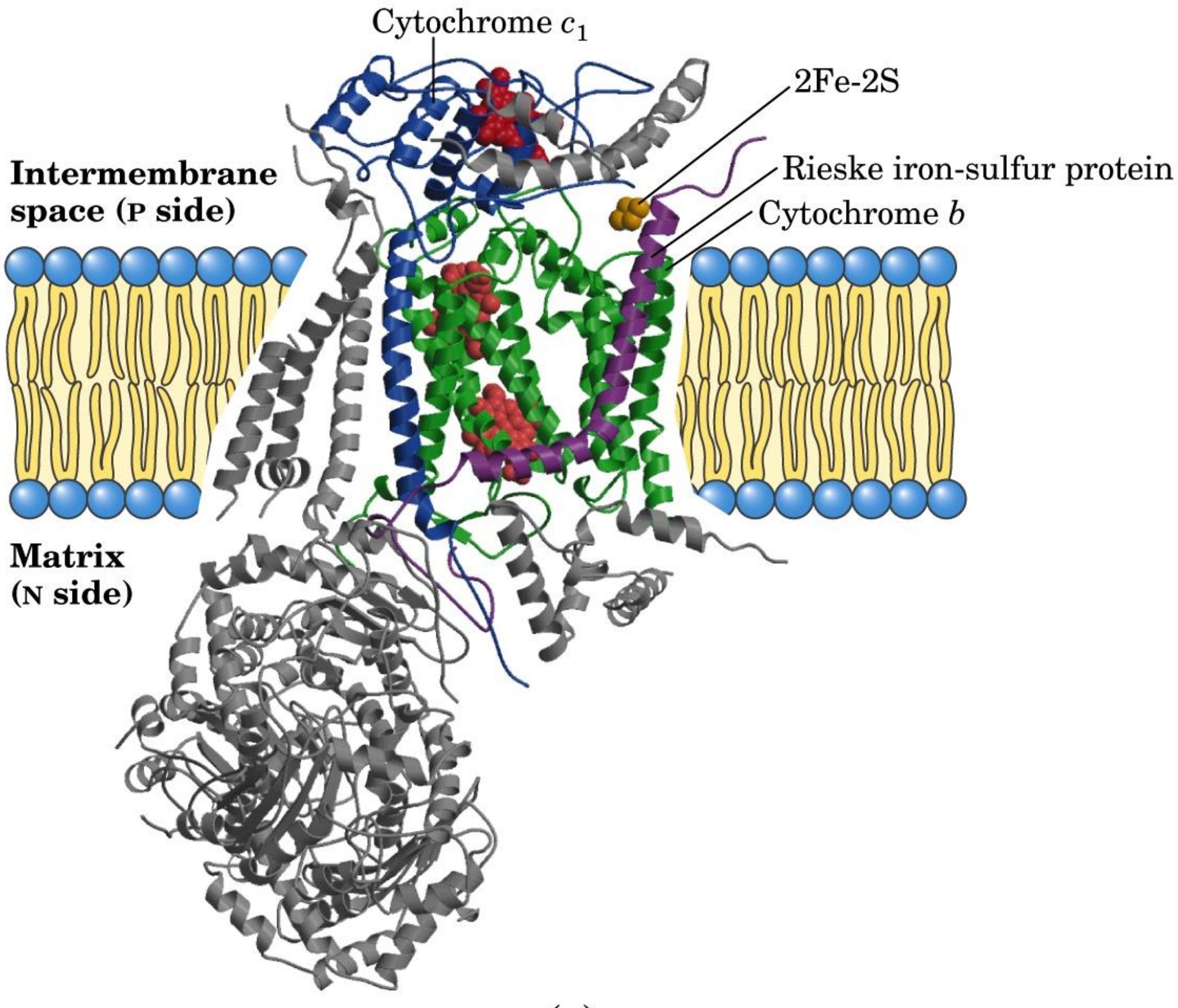
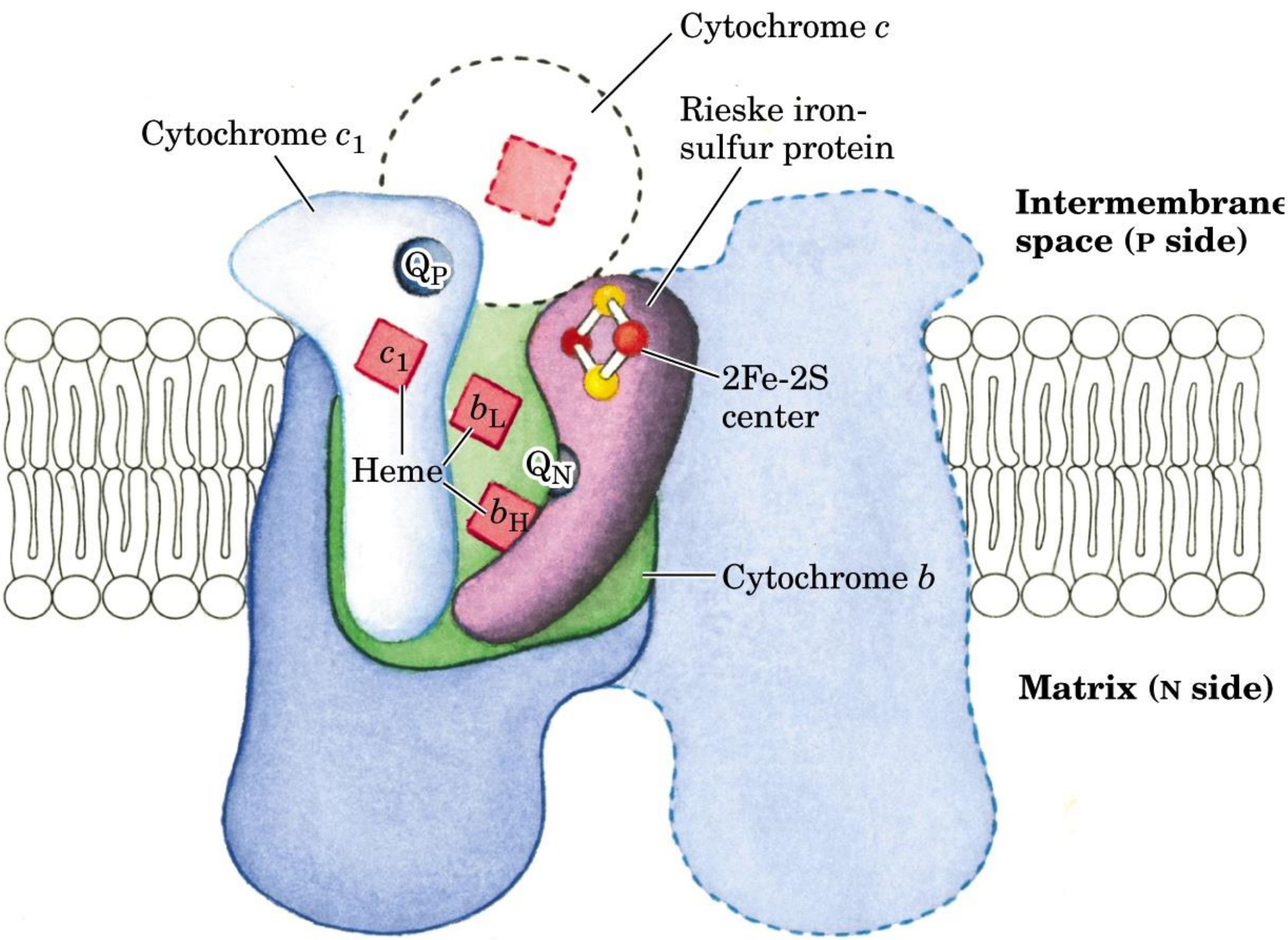
Complejo III: Ubiquinona:citocromo c oxidorreductasa

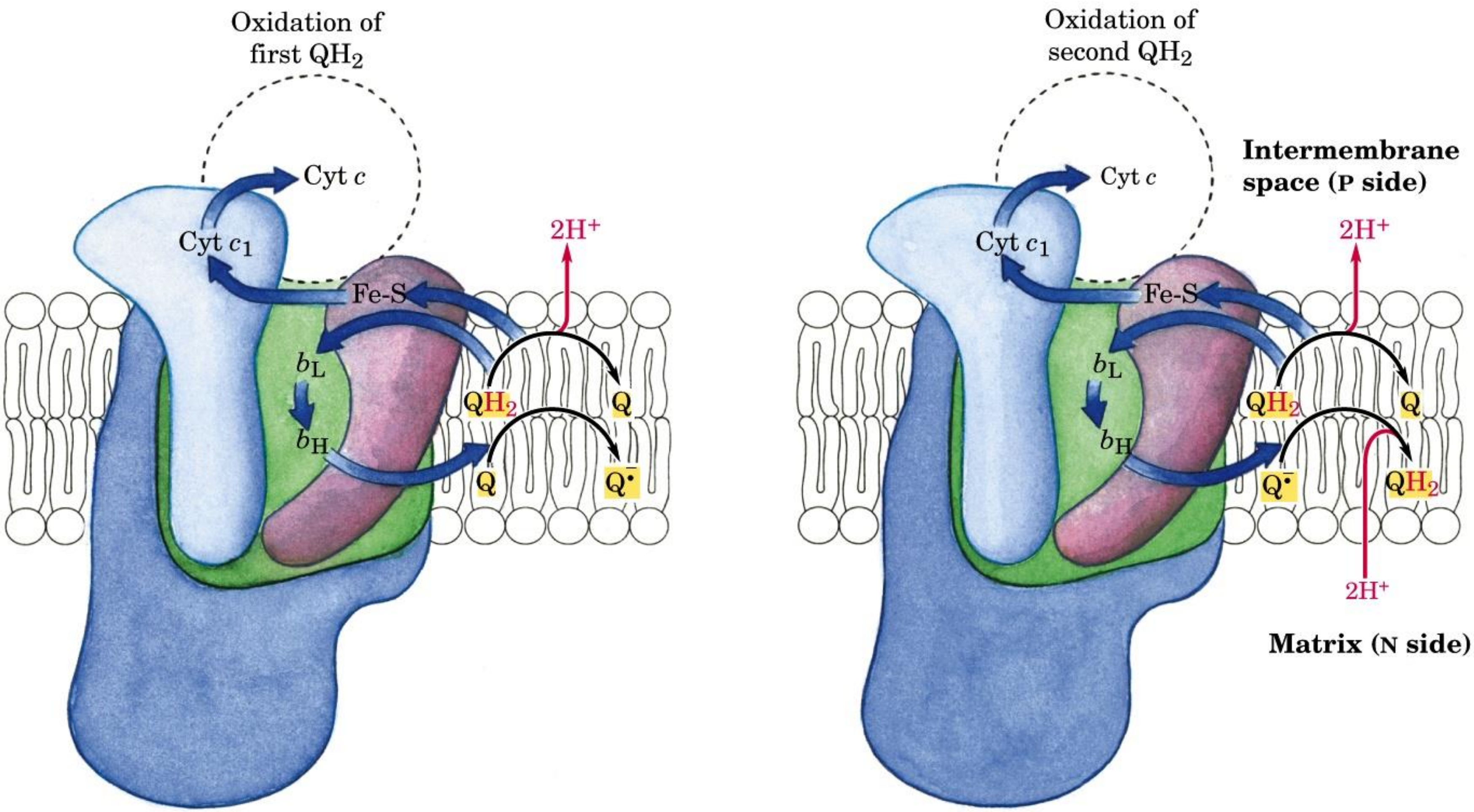


(a)



Cytochrome c
Rieske iron-sulfur protein
Cytochrome c_1
Intermembrane space (P side)
Q_P
c_1
b_L
2Fe-2S center
Heme
Q_N
b_H
Cytochrome b
Matrix (N side)

(b)



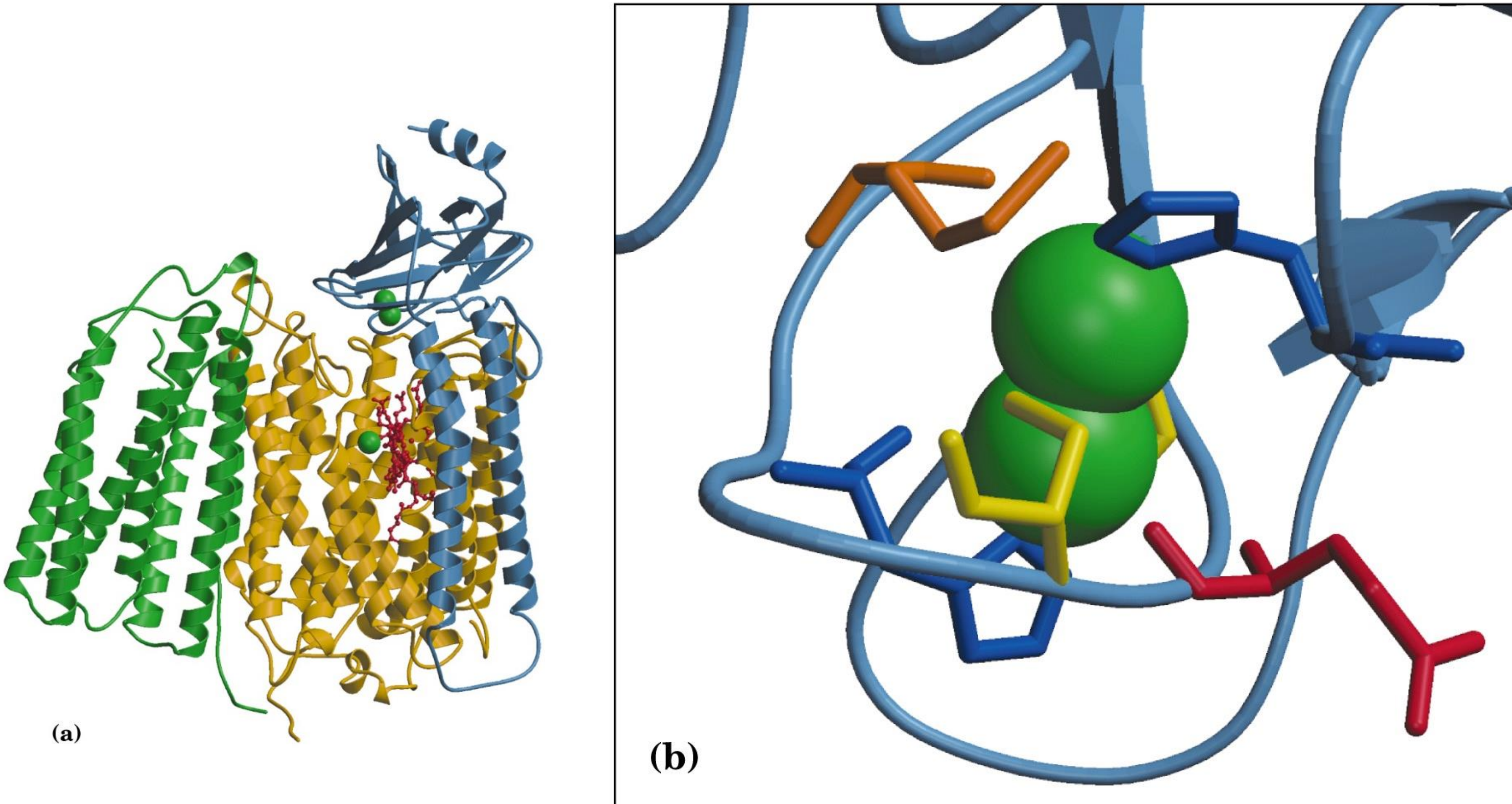
$$QH_2 + \text{Cyt } c_1 \text{ (oxidized)} \longrightarrow Q^{\bar{\bullet}} + 2H^+_P + \text{Cyt } c_1 \text{ (reduced)}$$

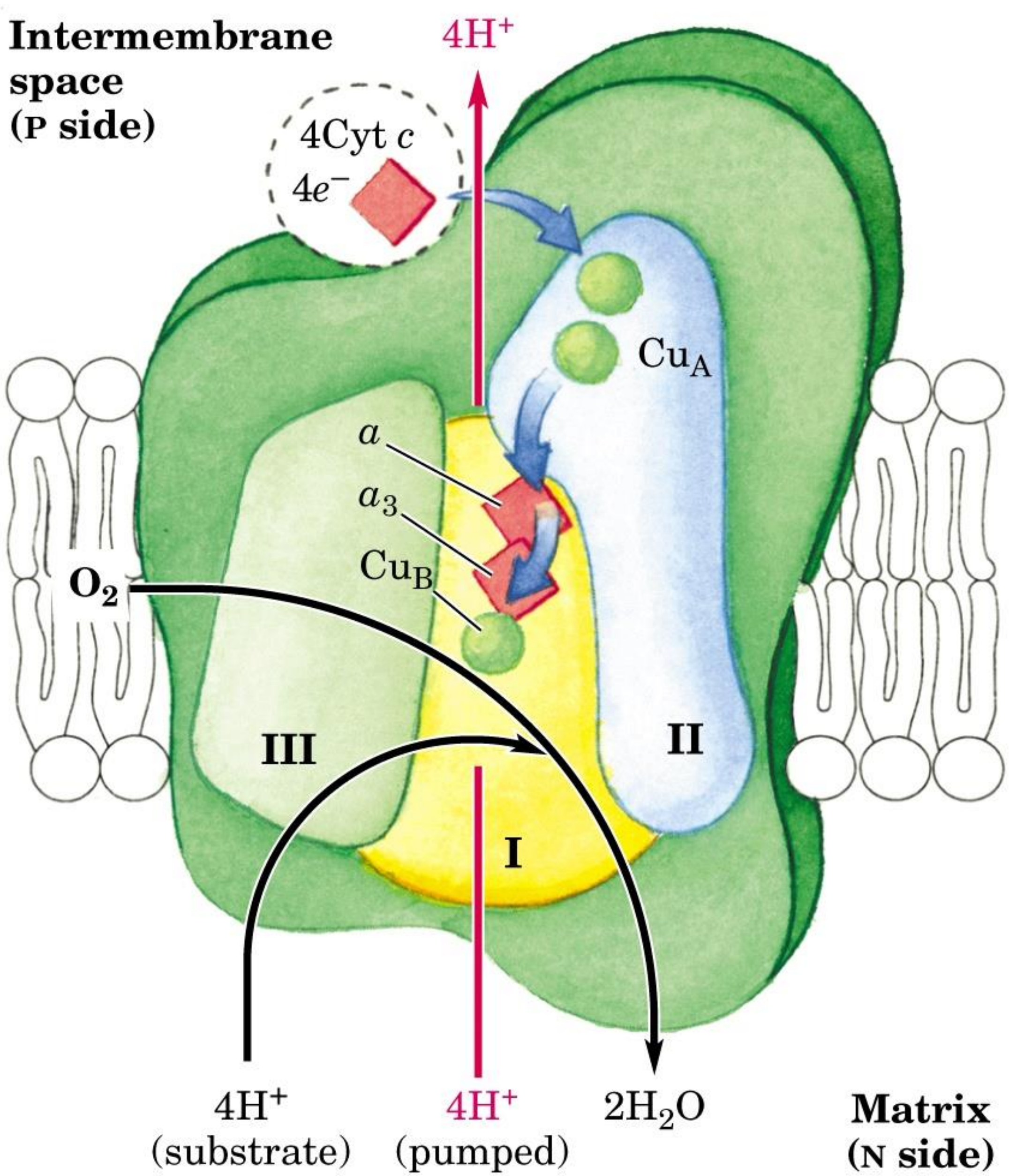
$$QH_2 + Q^{\bar{\bullet}} + 2H^+_N + \text{Cyt } c_1 \text{ (oxidized)} \longrightarrow QH_2 + 2H^+_P + Q + \text{Cyt } c_1 \text{ (reduced)}$$

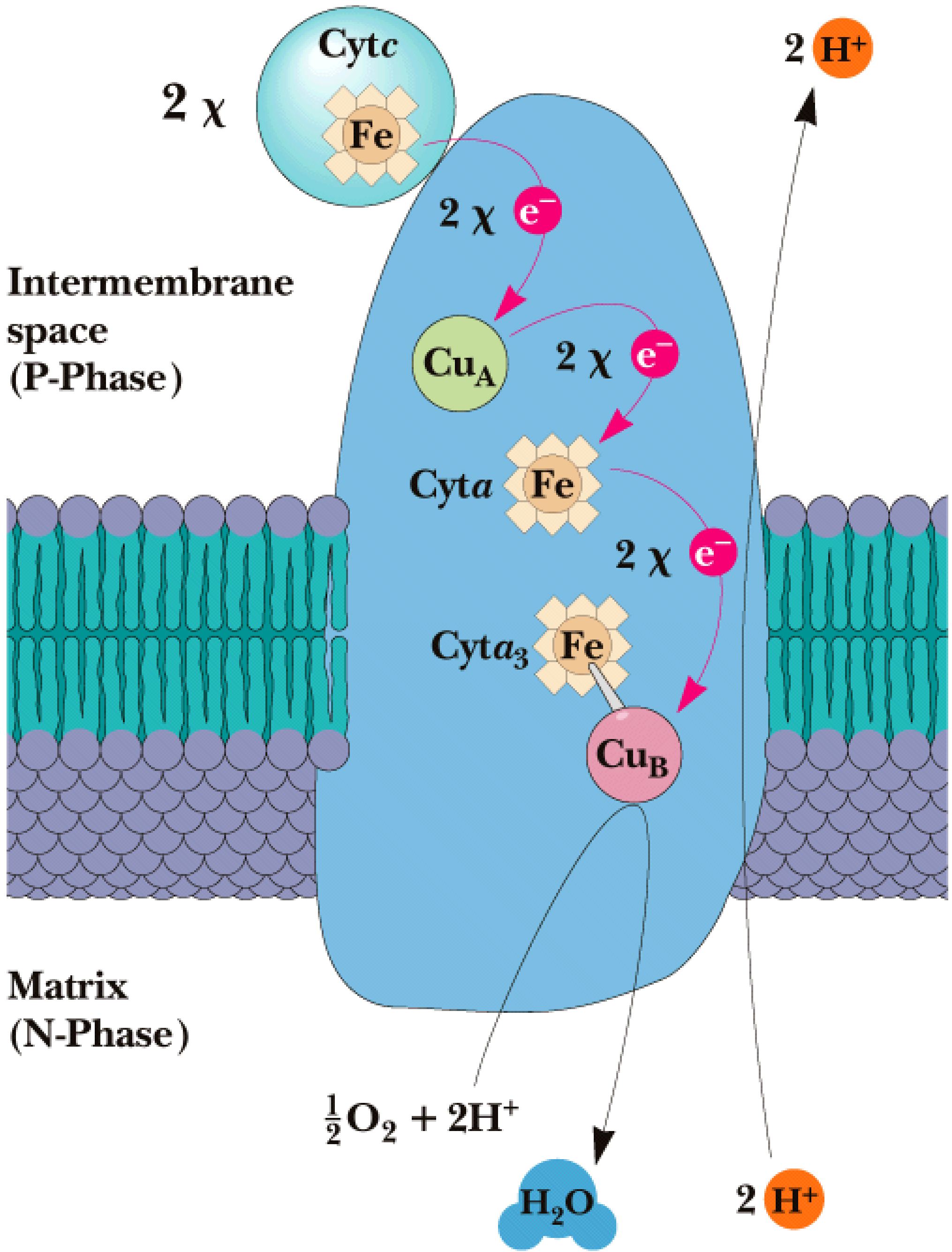
Net equation:

$$QH_2 + 2 \text{ Cyt } c_1 \text{ (oxidized)} + 2H^+_N \longrightarrow Q + 2 \text{ Cyt } c_1 \text{ (reduced)} + 4H^+_P$$

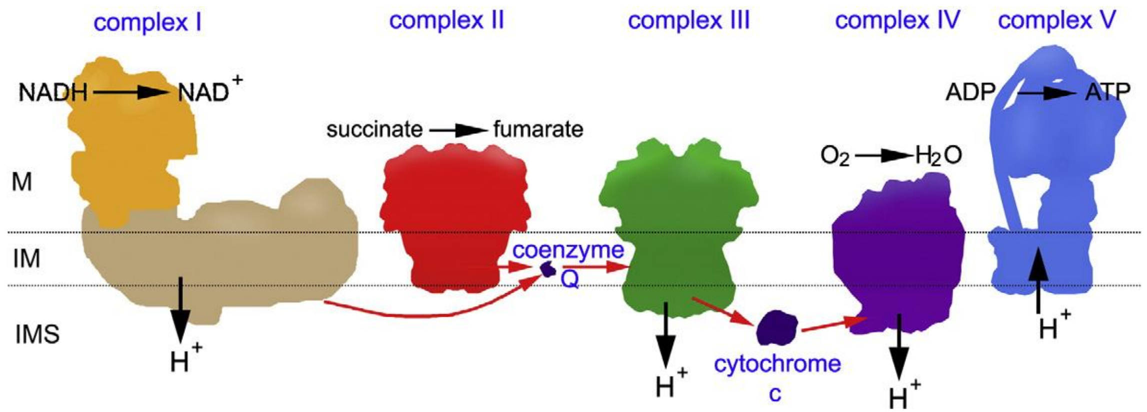
Complejo IV: Citocromo oxidasa




Intermembrane
space
(P side)
4H+
4Cyt c
4e−
CuA
a
a3
CuB
O2
III
II
I
4H+
(substrate)
4H+
(pumped)
2H2O
Matrix
(N side)



Cytc
2 χ
Fe
2 H+
2 χ e−
Intermembrane
space
(P-Phase)
CuA
2 χ e−
Cyta
Fe
2 χ e−
Cyta3
Fe
CuB
Matrix
(N-Phase)
½O2 + 2H+
H2O
2 H+



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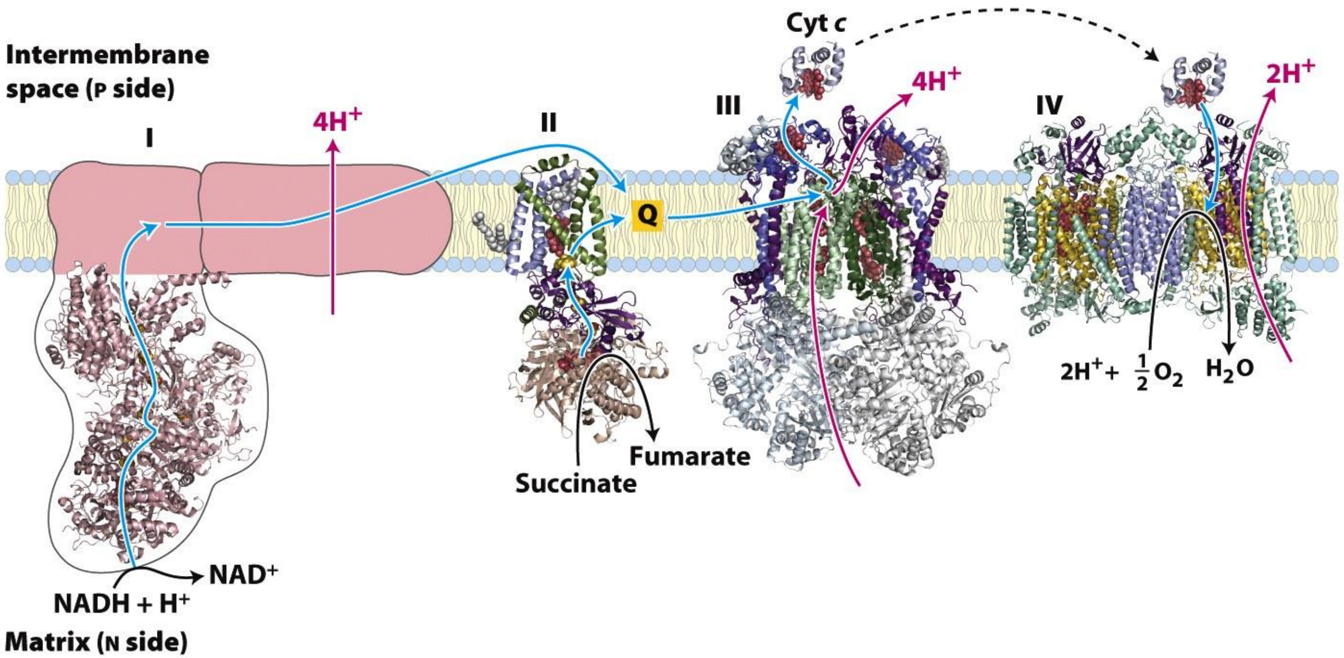

Figure 19-16
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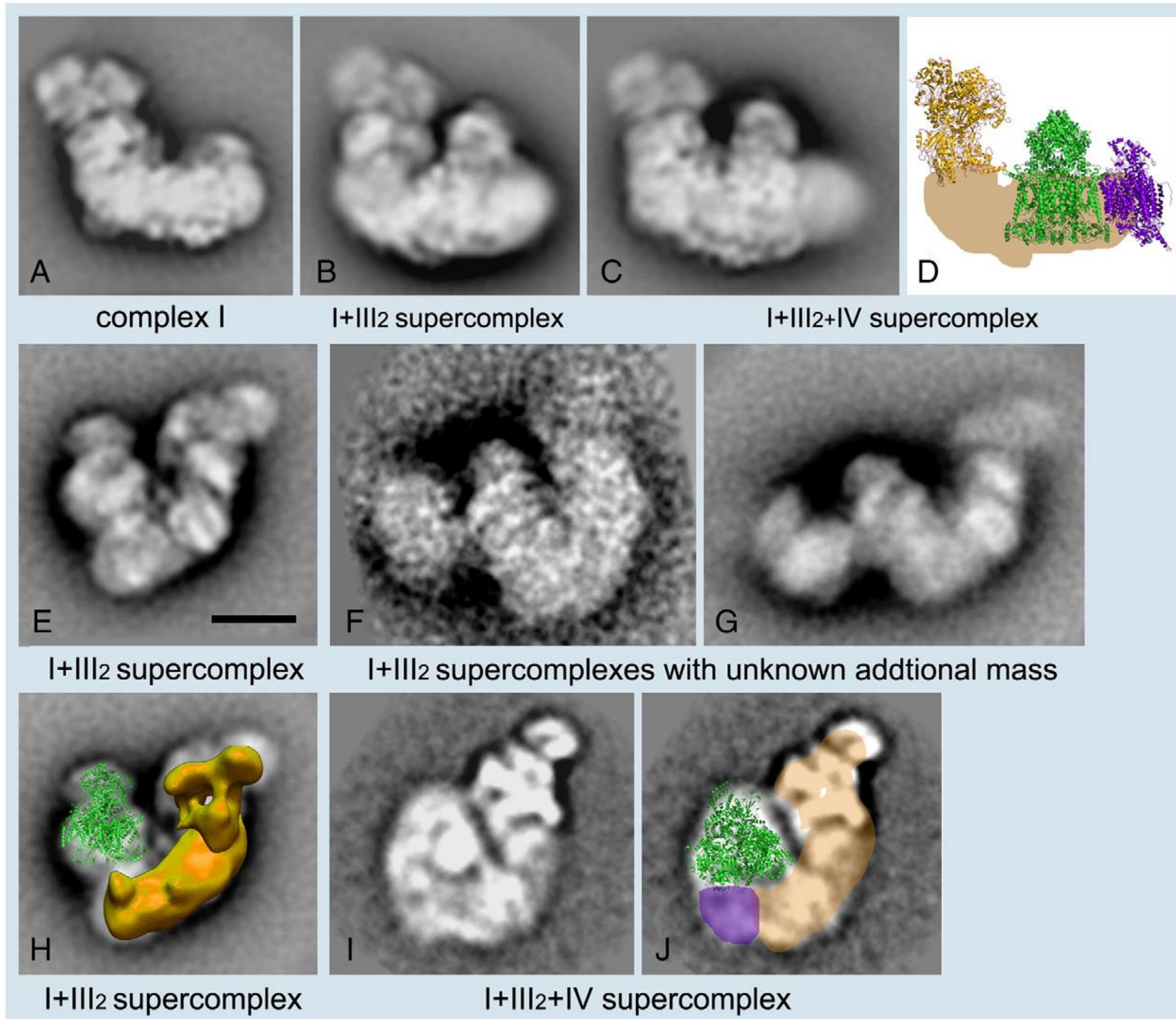
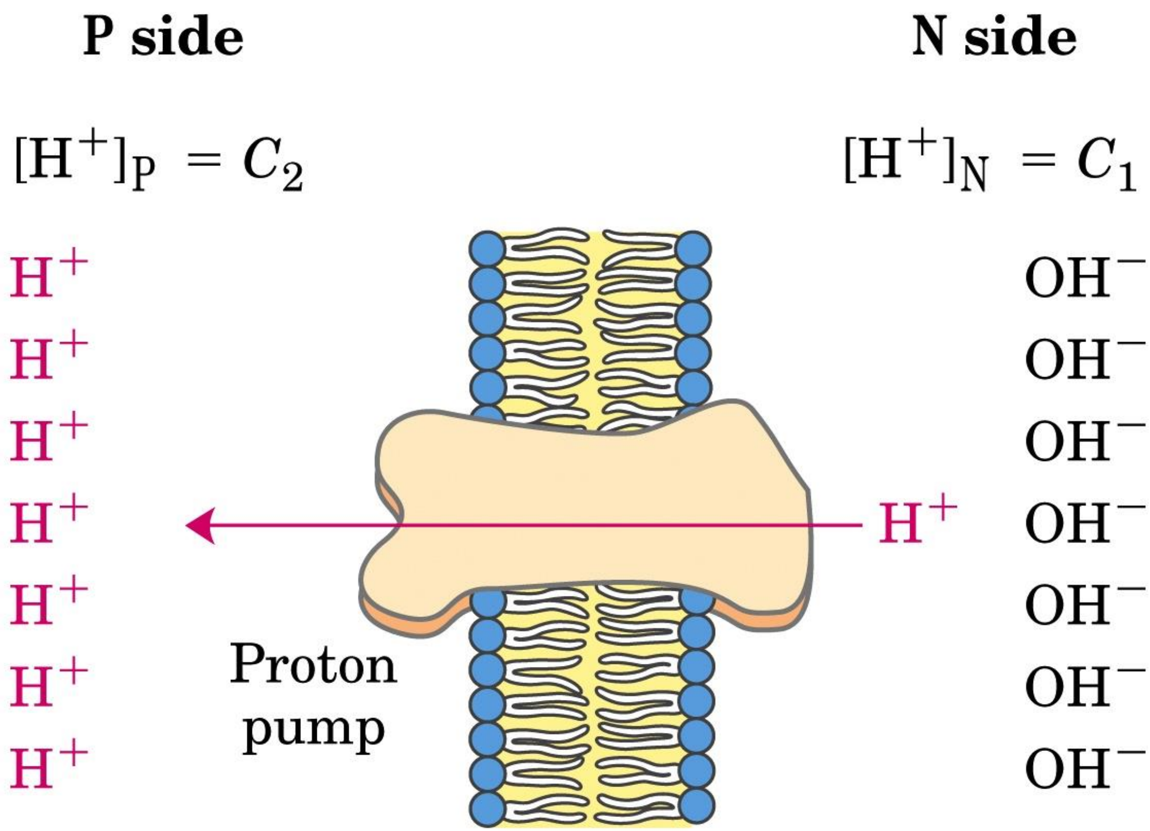


Fuerza protón-motriz



$$\Delta G = RT \ln (C_2/C_1) + Z\mathcal{F}\Delta\psi$$
$$= 2.3RT\,\Delta pH + \mathcal{F}\Delta\psi$$

Síntesis de ATP

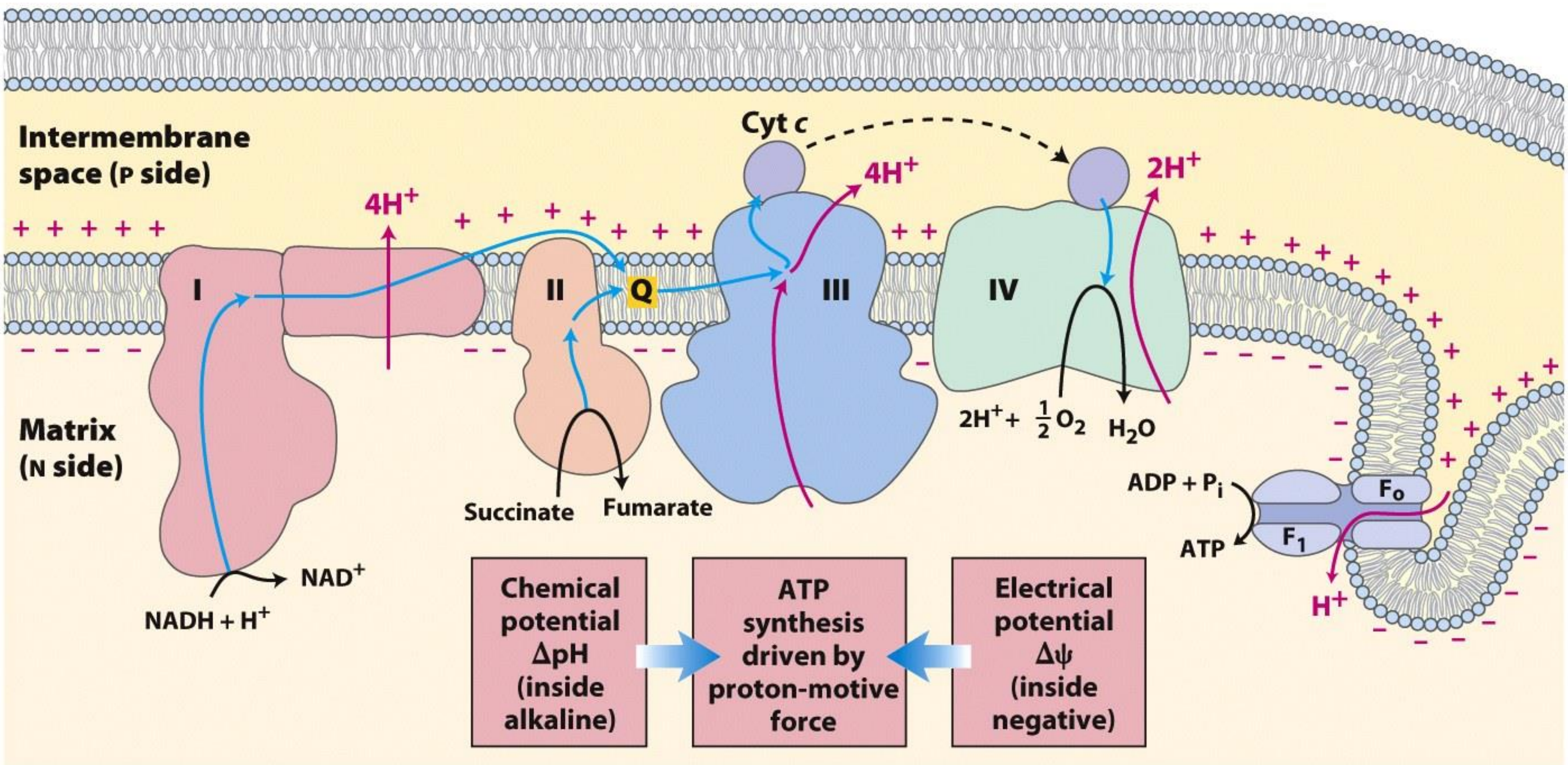
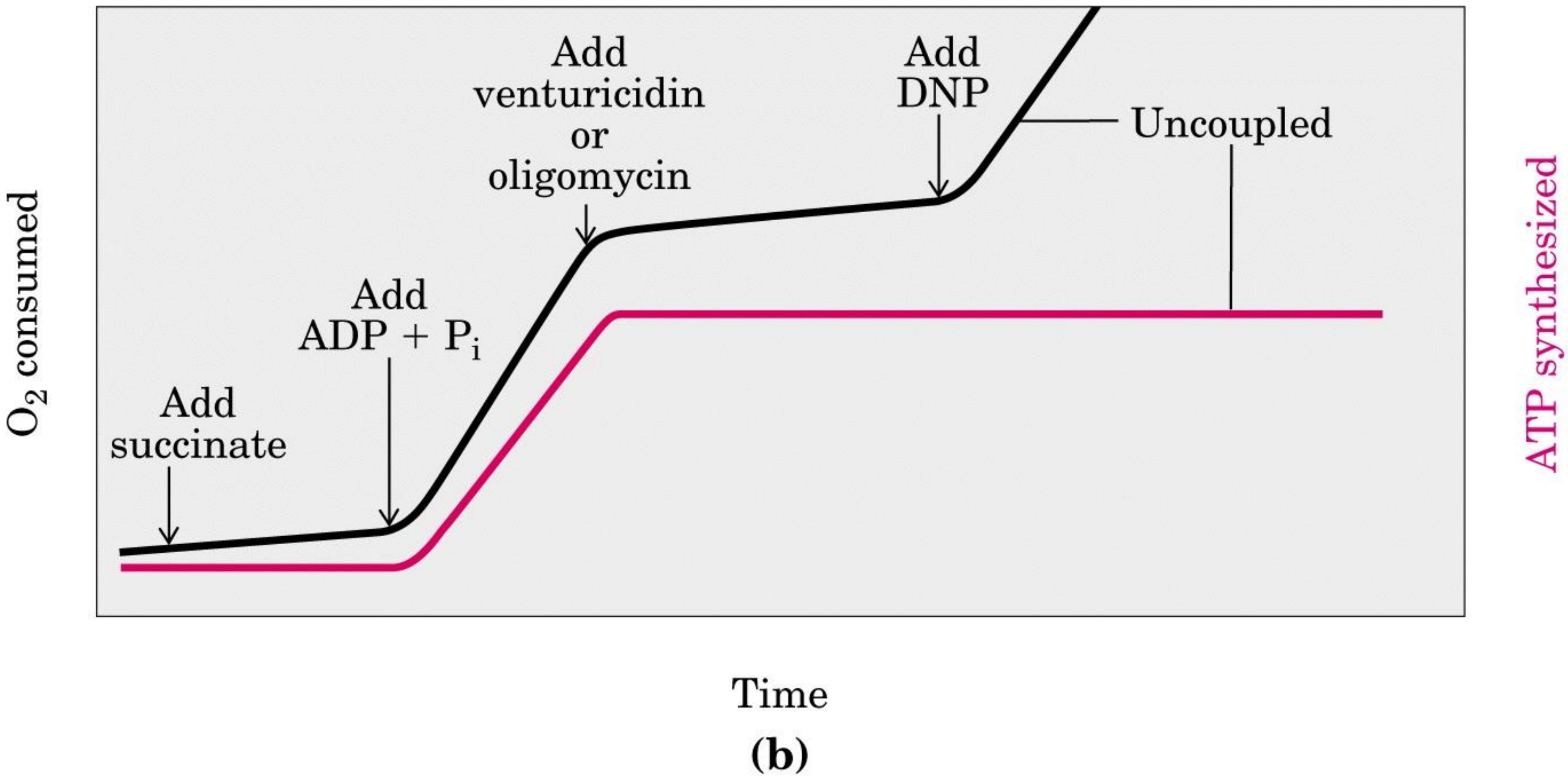


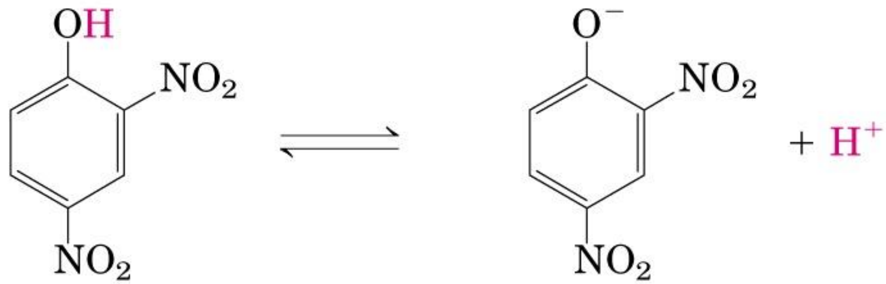
Figure 19-19
Lehninger Principles of Biochemistry, Fifth Edition

$$ADP + Pi + nH_P^+ \rightarrow ATP + H_2O + nH_N^+$$

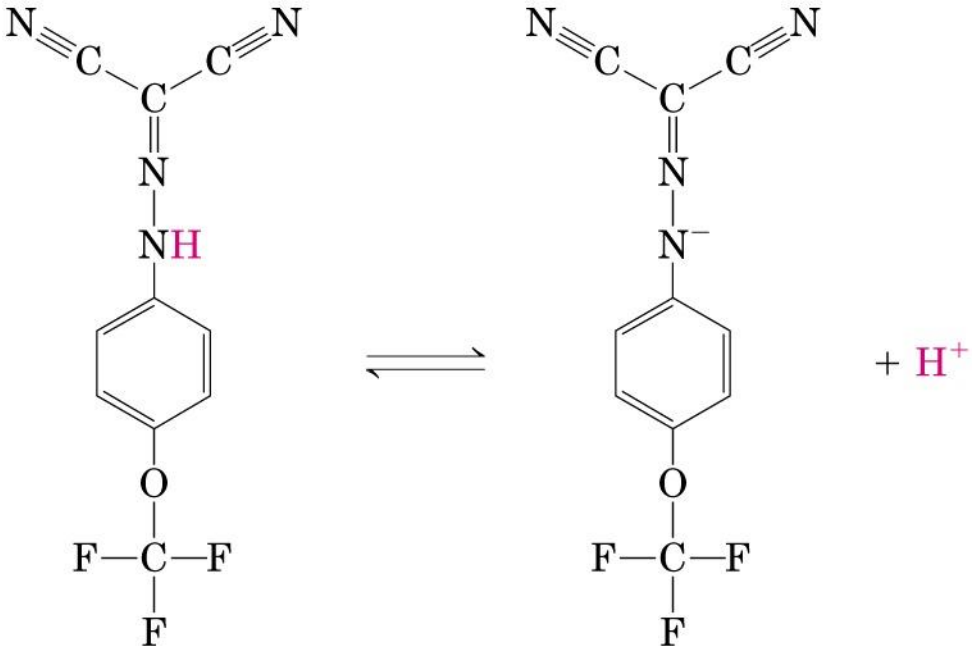
Síntesis de ATP



Desacoplantes químicos de la fosforilación oxidativa



2,4-Dinitrophenol
(DNP)



Carbonylcyanide-*p*-
trifluoromethoxyphenylhydrazone
(FCCP)

Tipos de ATPasas

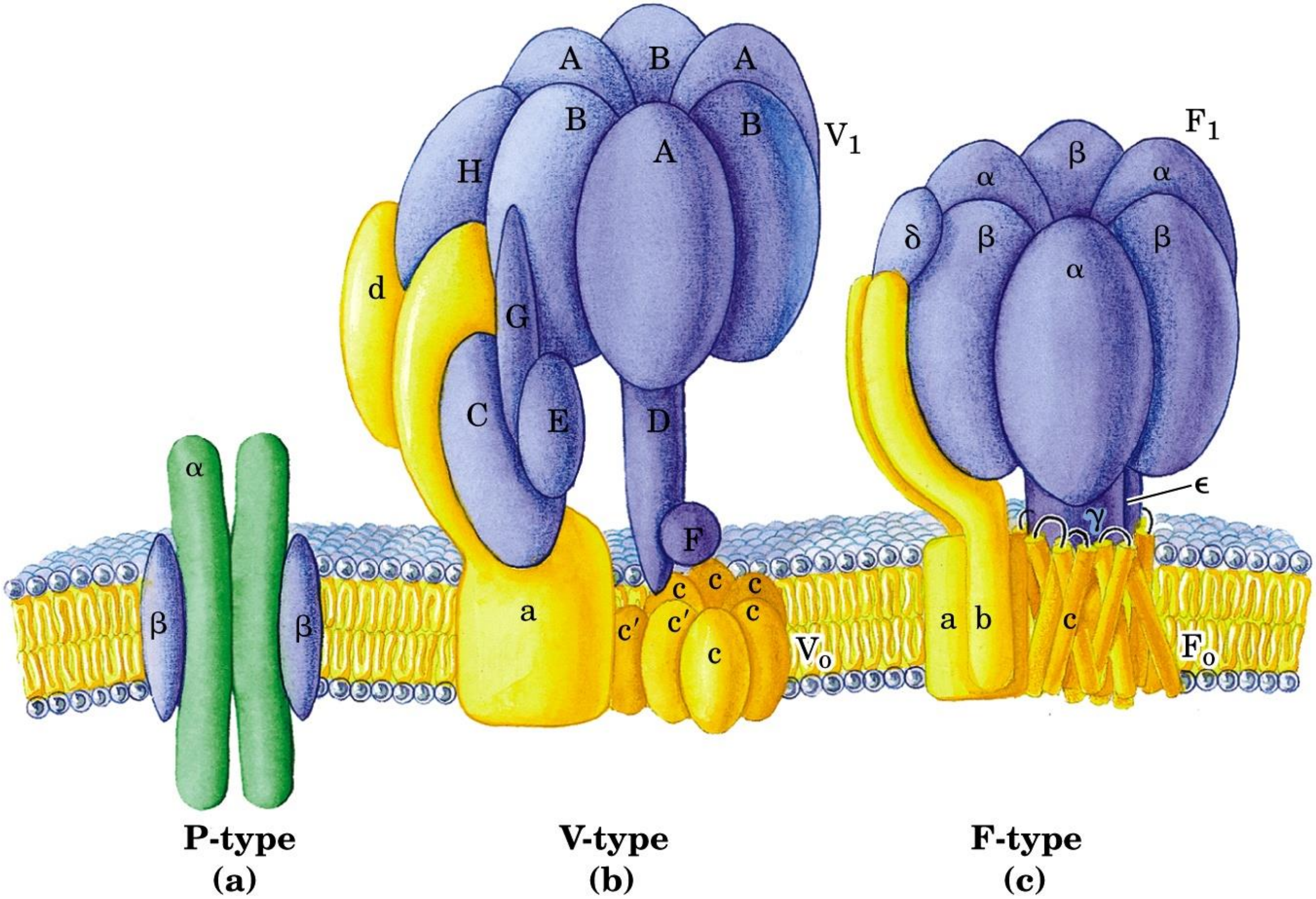
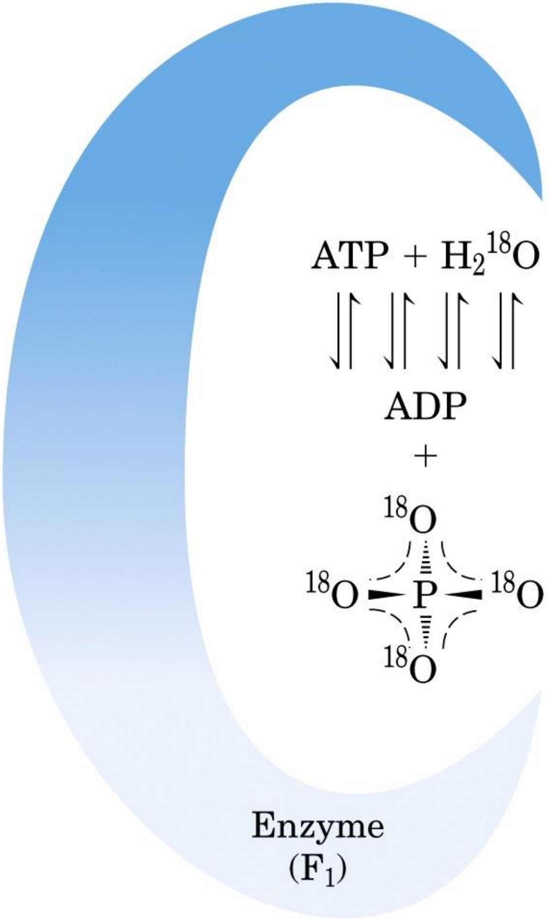


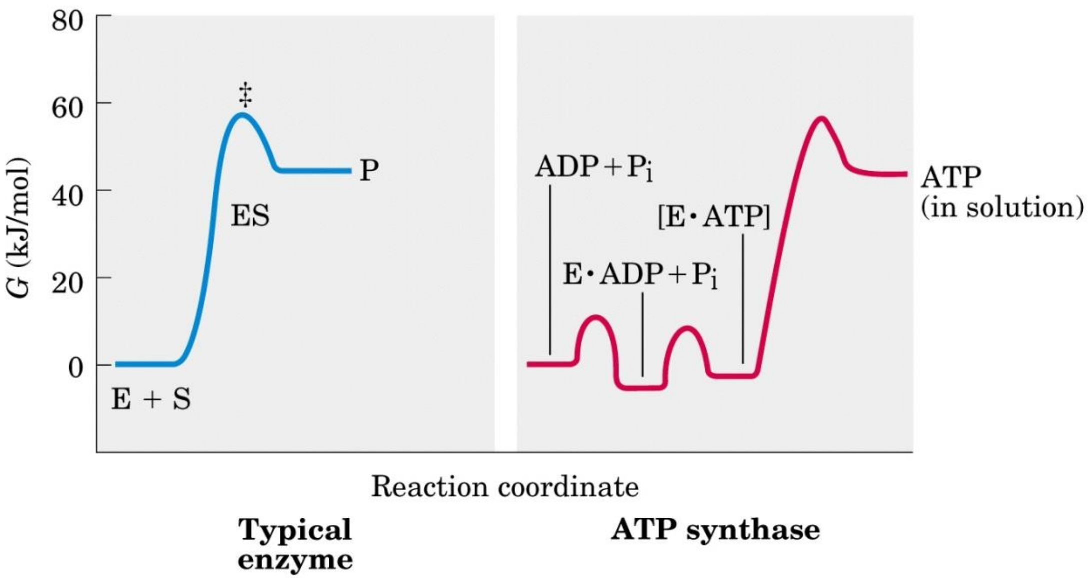
table 12–4

Four Classes of Transport ATPases

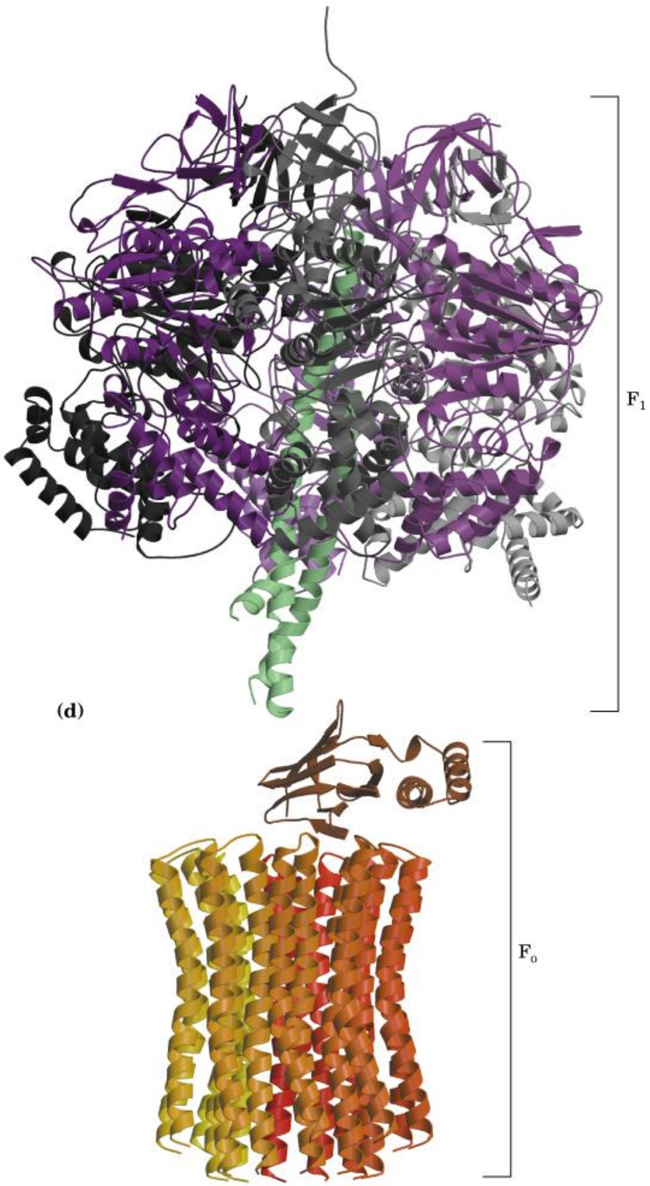
	Organism or tissue	Type of membrane	Role of ATPase
P-type ATPases			
$Na^{+}K^{+}$	Animal tissues	Plasma	Maintains low $[Na^{+}]$, high $[K^{+}]$ inside cell; creates transmembrane electrical potential
$H^{+}K^{+}$	Acid-secreting (parietal) cells of mammals	Plasma	Acidifies contents of stomach
H^{+}	Fungi *(Neurospora)*	Plasma	Create H^{+} gradient to drive secondary transport of extracellular solutes into cell
H^{+}	Higher plants	Plasma	
Ca^{2+}	Animal tissues	Plasma	Maintains low $[Ca^{2+}]$ in cytosol
Ca^{2+}	Myocytes of animals	Sarcoplasmic reticulum (endoplasmic reticulum)	Sequesters intracellular Ca^{2+}, keeping cytosolic $[Ca^{2+}]$ low
Cd^{2+}, Hg^{2+}, Cu^{2+}	Bacteria	Plasma	Pumps heavy metal ions out of cell
V-type ATPases			
H^{+}	Animals	Lysosomal, endosomal, secretory vesicles	Create low pH in compartment, activating proteases and other hydrolytic enzymes
H^{+}	Higher plants	Vacuolar	
H^{+}	Fungi	Vacuolar	
F-type ATPases			
H^{+}	Eukaryotes	Inner mitochondrial	Catalyze formation of ATP from ADP + P_i
H^{+}	Higher plants	Thylakoid	
H^{+}	Prokaryotes	Plasma	
Multidrug transporter			
	Animal tumor cells	Plasma	Removes a wide variety of hydrophobic natural products and synthetic drugs from cytosol, including vinblastine, doxorubicin, actinomycin D, mitomycin, taxol, colchicine, and puromycin

Mecanismo catalítico de F_1





Estructura de la F_oF_1 ATPasas/ATP sintasa



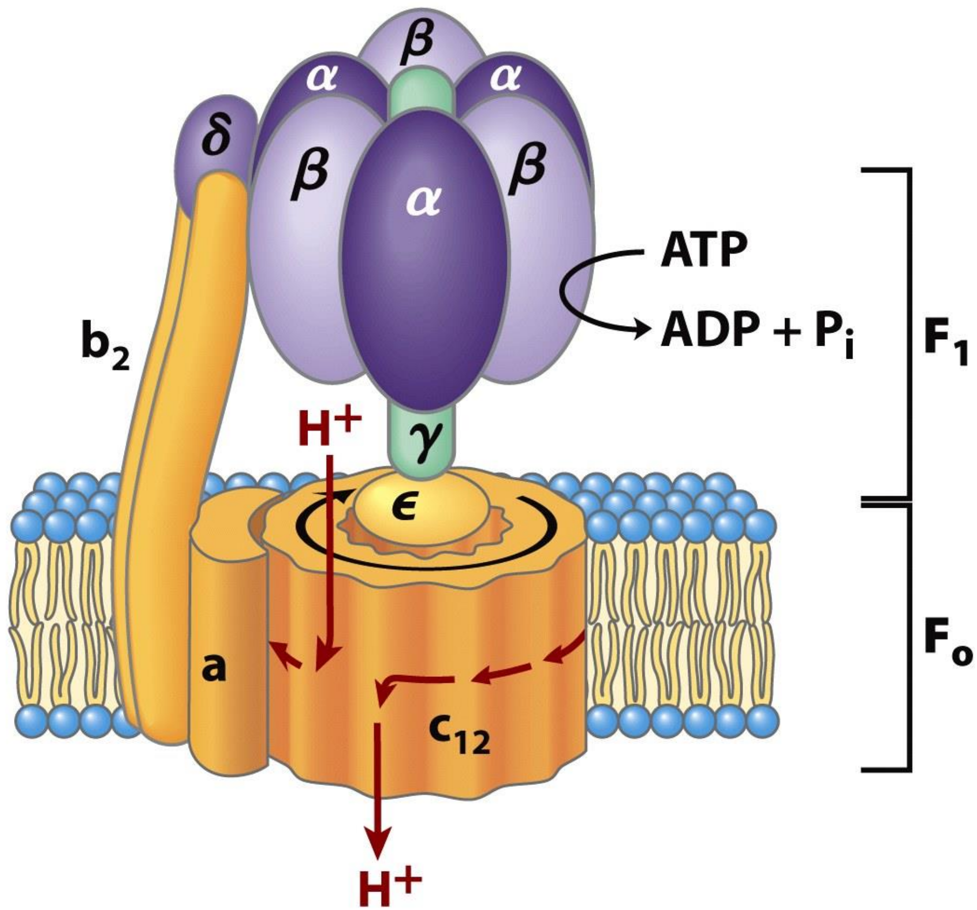
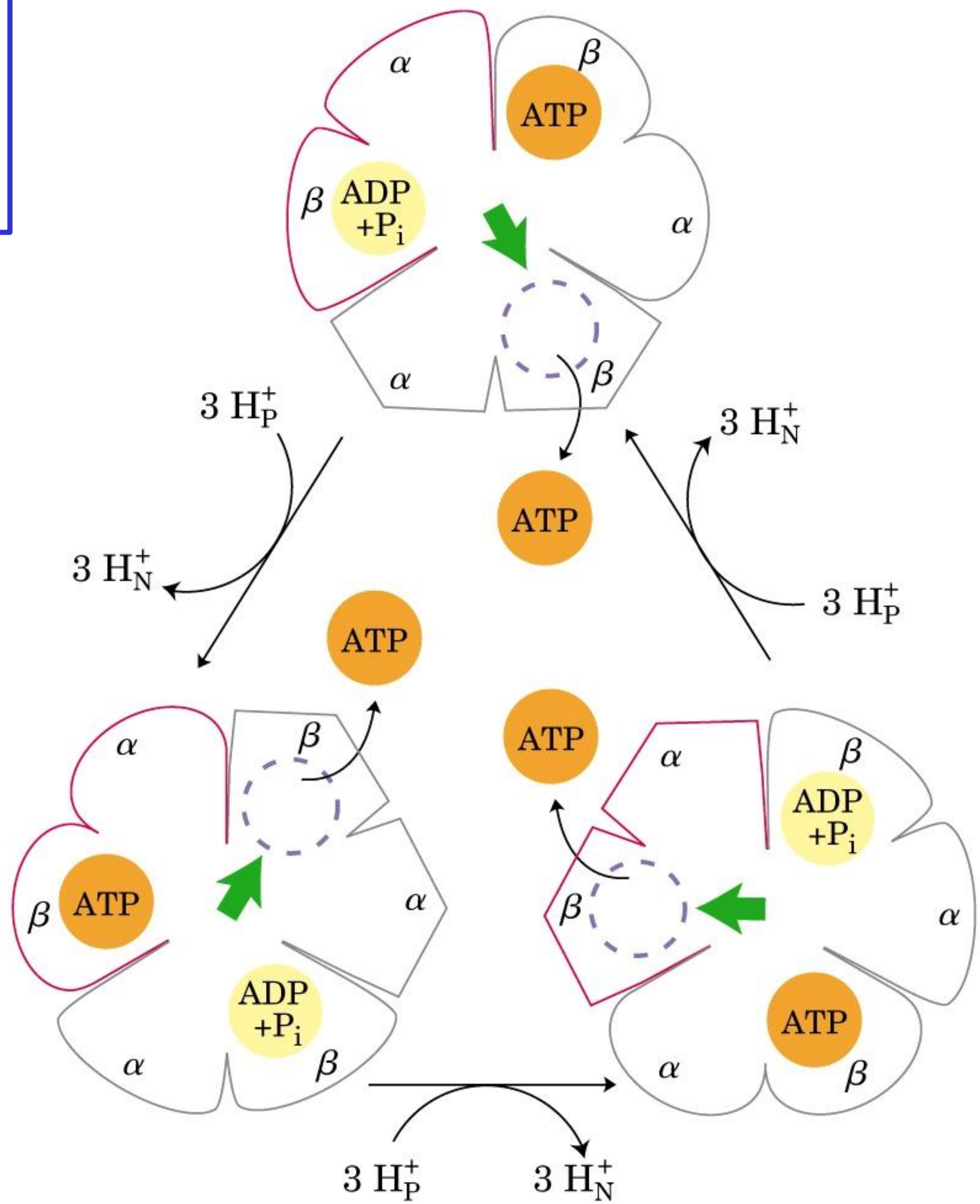
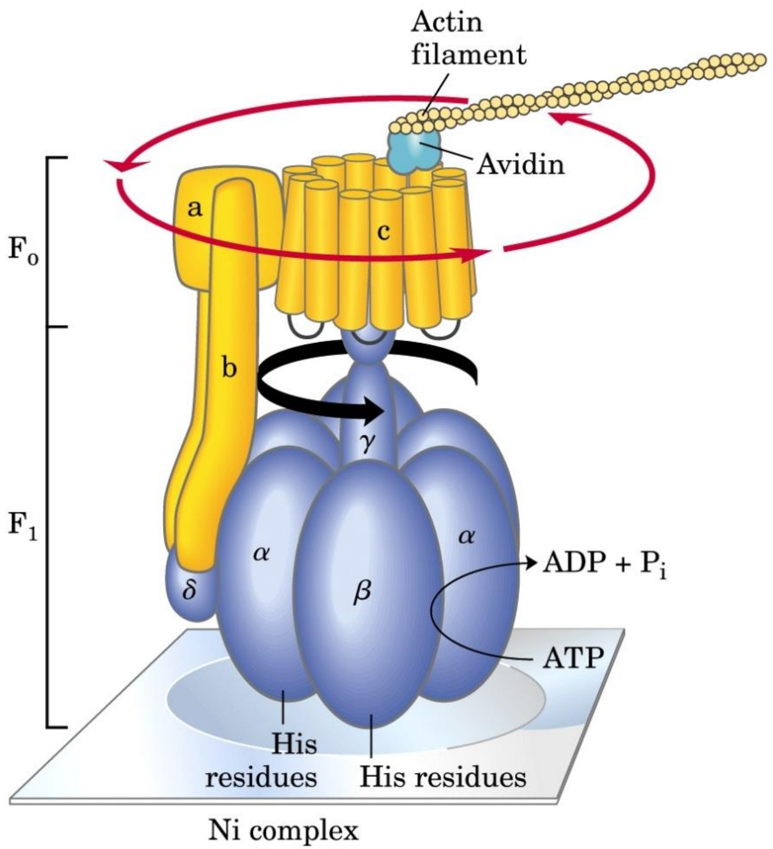


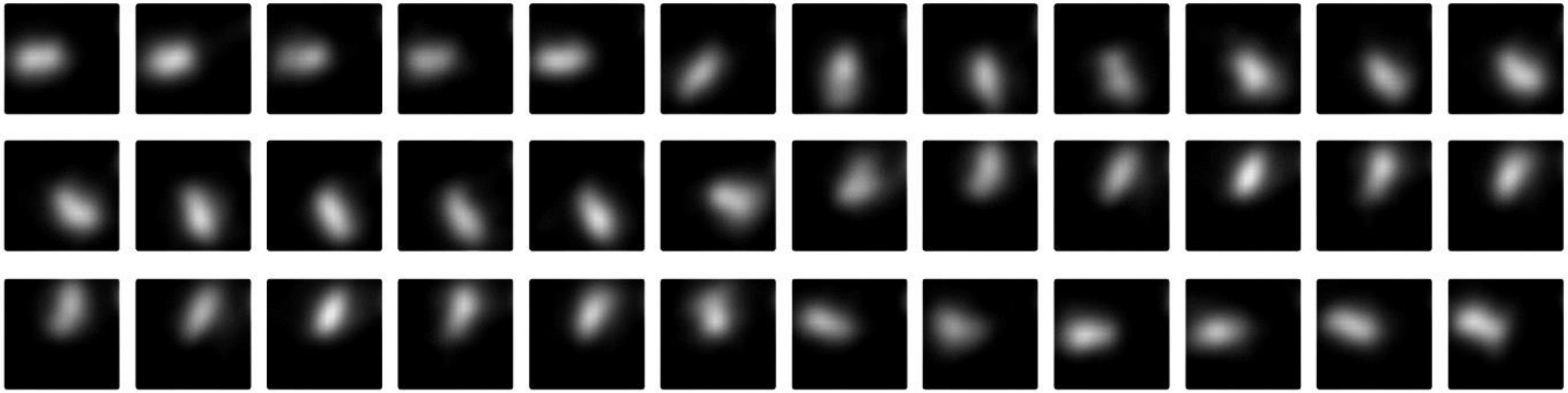
Figure 11-39
Lehninger Principles of Biochemistry, Fifth Edition

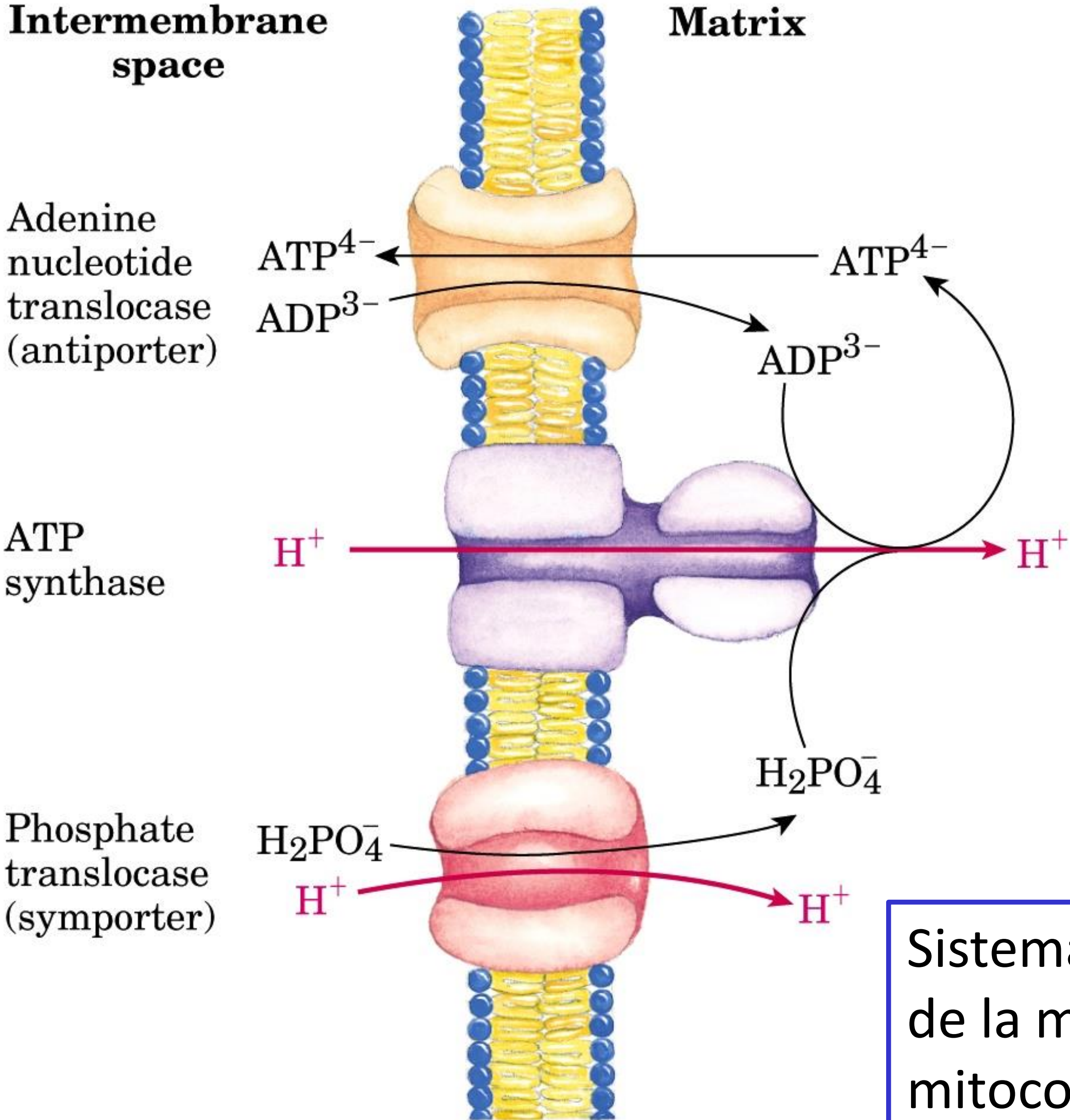
Modelo de unión y cambio de la ATP sintetasa





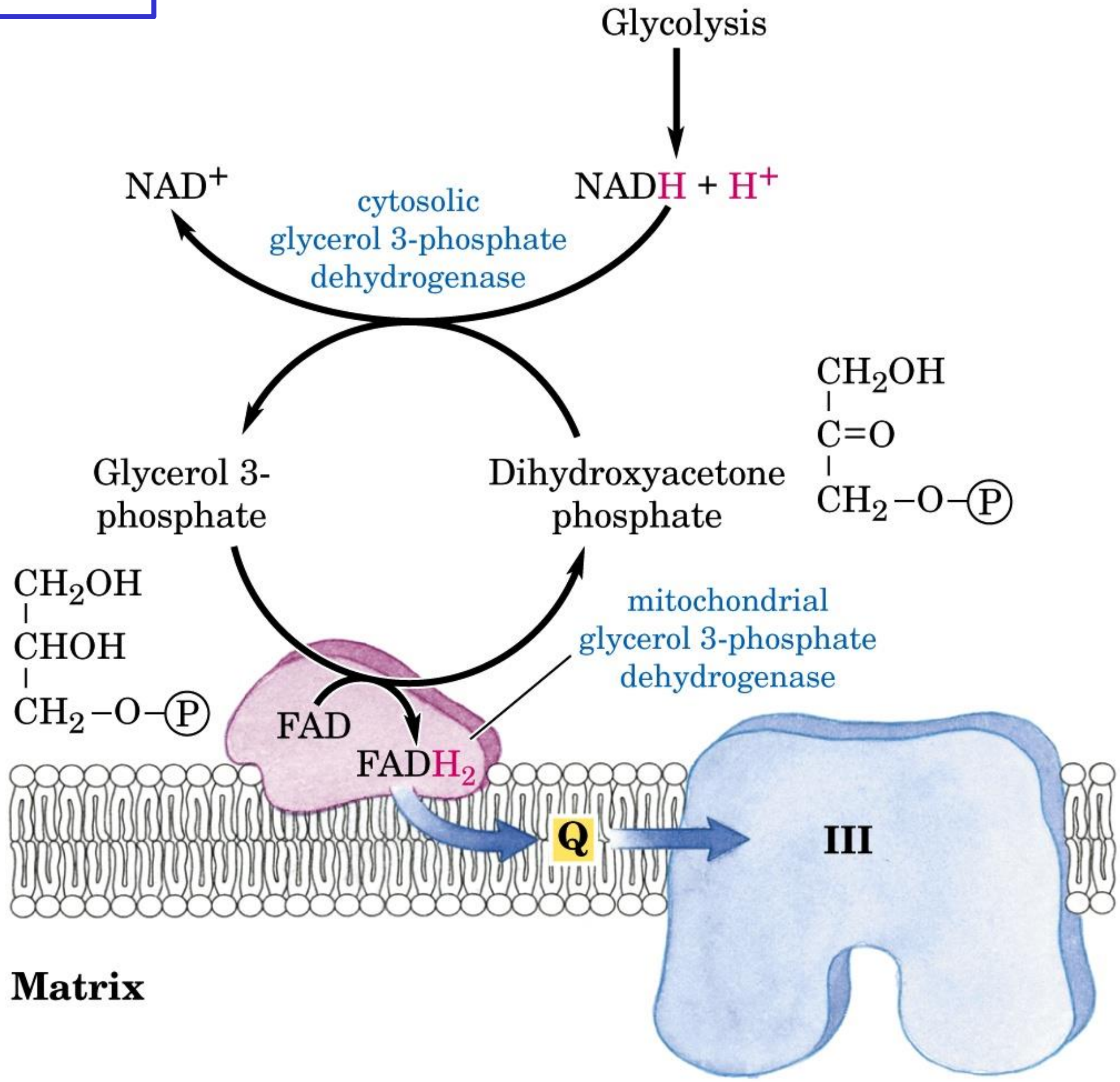
Demostración experimental de la rotación de F_o





Sistemas de transporte de la membrana mitocondrial interna

Lanzadera del glicerol-3-fosfato



OXIDACIÓN TOTAL DE LA GLUCOSA

TABLE 19–5 ATP Yield from Complete Oxidation of Glucose

Process	Direct product	Final ATP
Glycolysis	2 NADH (cytosolic)	3 or 5*
	2 ATP	2
Pyruvate oxidation (two per glucose)	2 NADH (mitochondrial matrix)	5
Acetyl-CoA oxidation in citric acid cycle (two per glucose)	6 NADH (mitochondrial matrix)	15
	2 $FADH_2$	3
	2 ATP or 2 GTP	2
Total yield per glucose		30 or 32

*The number depends on which shuttle system transfers reducing equivalents into the mitochondrion.

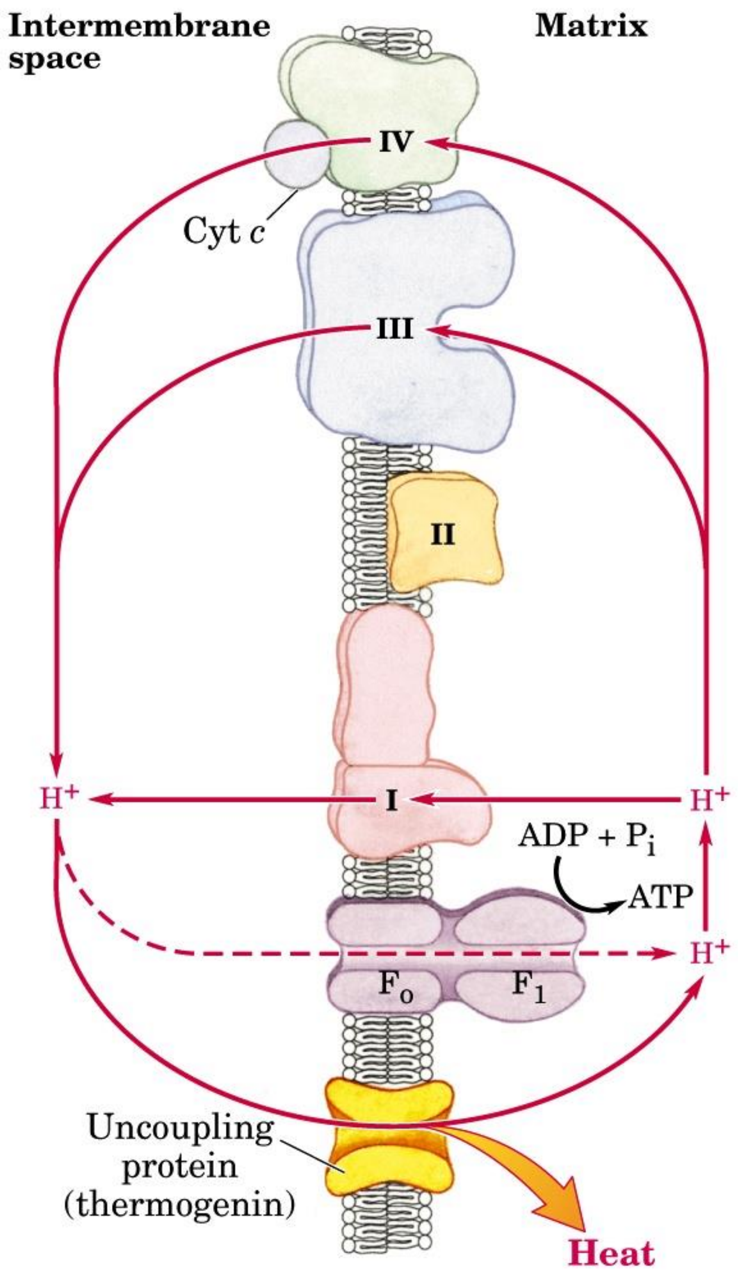
Table 19-5
Lehninger Principles of Biochemistry, Fifth Edition

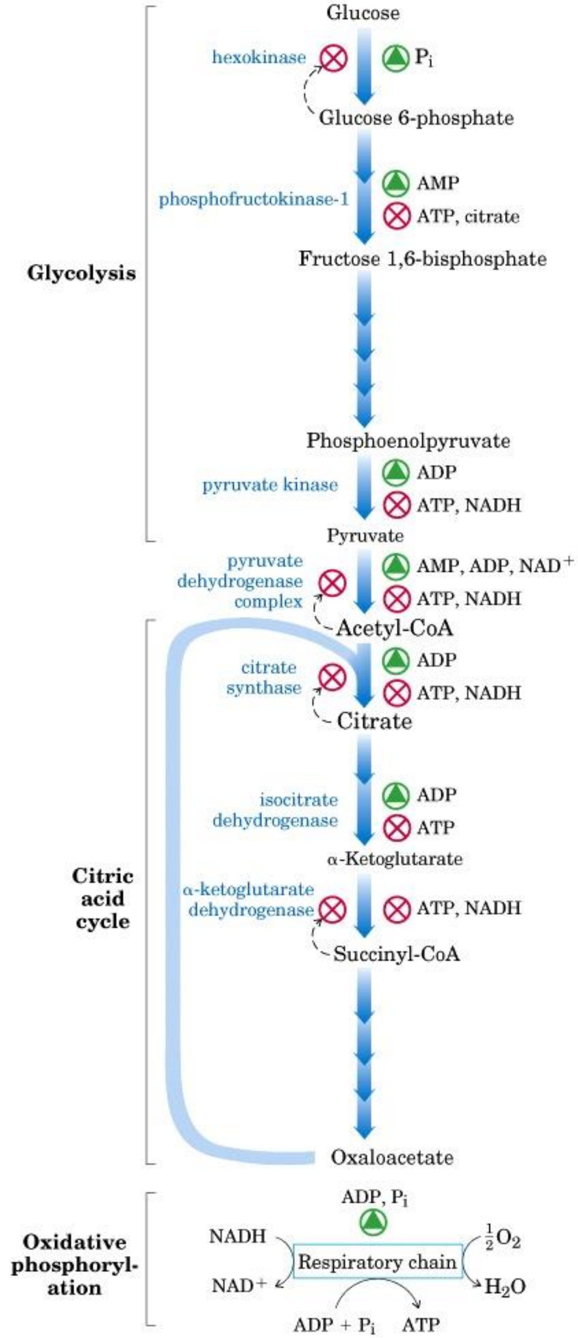
Balance energético de la oxidación de acetato a CO_2

CAT		Te⁻ y FO		Generación
3 NADH + H^+	x	2.5 ATP	→	7.5 ATP
1 $FADH_2$	x	1.5 ATP	→	1.5 ATP
1 GTP (ATP)			→	1 ATP

Por vuelta del ciclo/ 2 descarboxilaciones 10 ATP

Generación de calor por las mitocondrias desacopladas




Glycolysis
Glucose
hexokinase
P_i
Glucose 6-phosphate
phosphofructokinase-1
AMP
ATP, citrate
Fructose 1,6-bisphosphate
Phosphoenolpyruvate
pyruvate kinase
ADP
ATP, NADH
Pyruvate
pyruvate dehydrogenase complex
AMP, ADP, NAD^+
ATP, NADH
Acetyl-CoA
Citric acid cycle
citrate synthase
ADP
ATP, NADH
Citrate
isocitrate dehydrogenase
ADP
ATP
α-Ketoglutarate
α-ketoglutarate dehydrogenase
ATP, NADH
Succinyl-CoA
Oxaloacetate
Oxidative phosphorylation
ADP, P_i
NADH
NAD^+
Respiratory chain
$\frac{1}{2}O_2$
H_2O
ADP + P_i
ATP

Lectura suplementaria sobre supercomplejos

Supercomplex Assembly Determines Electron flux in the Mitochondrial Electron Transport Chain
Lapuente-Brun, E., *et al*. *Science* **340**, 1567 (2013)