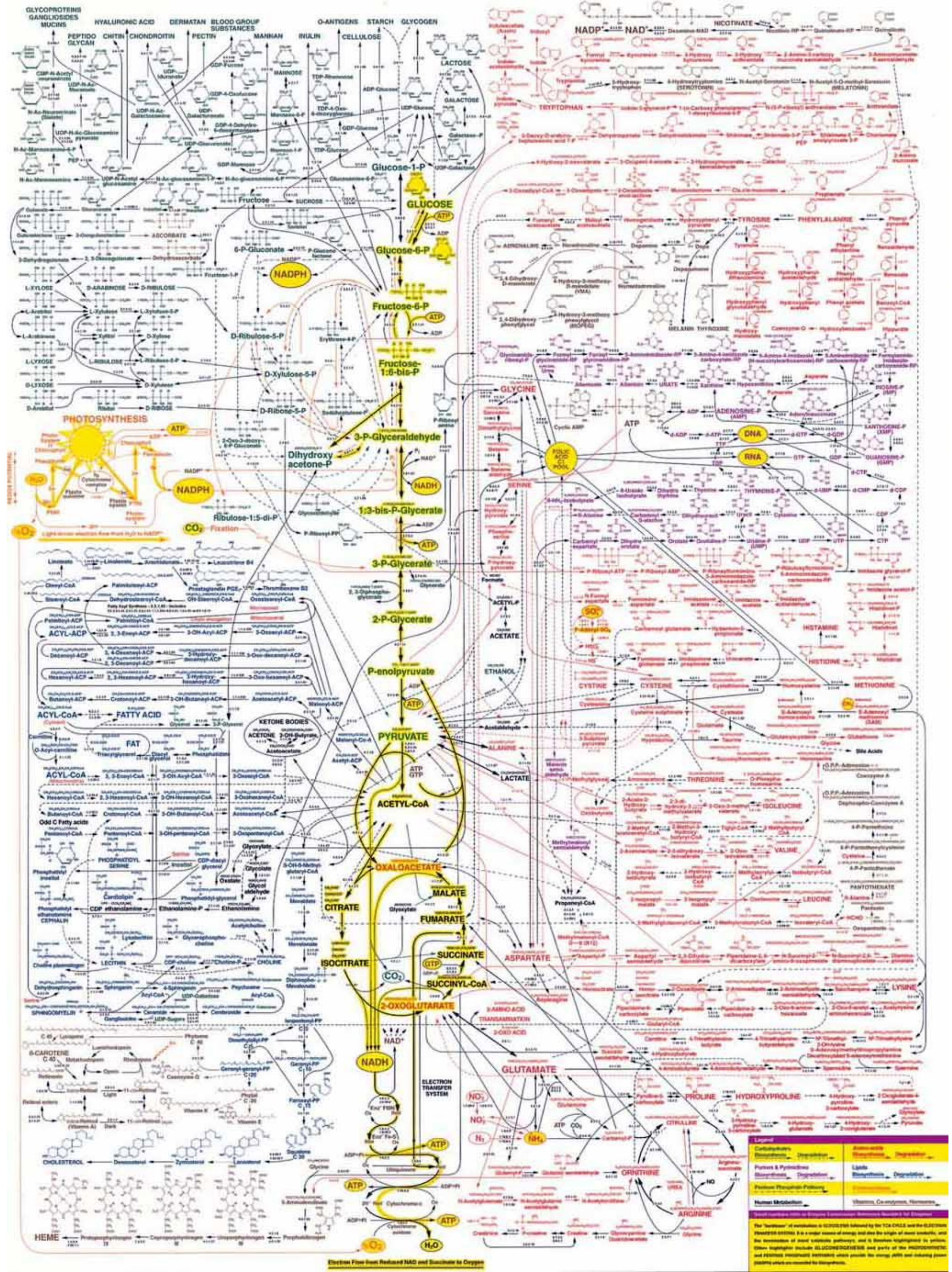
Ciclo del Ácido Cítrico
o
Ciclo de Krebs

Marco Galleguillos Caamaño

Bases Moleculares y Celulares
del Organismo Animal


GLYCOPROTEINS GANGLIOSIDES MUCINS
PEPTIDO GLYCAN
HYALURONIC ACID
CHITIN
CHONDROITIN
DERMATAN
PECTIN
BLOOD GROUP SUBSTANCES
MANNAN
INULIN
O-ANTIGENS
STARCH
CELLULOSE
GLYCOGEN
LACTOSE
GALACTOSE
Glucose-1-P
GLUCOSE
ATP
ADP
Glucose-6-P
NADPH
Fructose-6-P
Fructose-1:6-bis-P
D-Ribulose-5-P
D-Xylulose-5-P
D-Ribose-5-P
PHOTOSYNTHESIS
3-P-Glyceraldehyde
Dihydroxy acetone-P
NADH
1:3-bis-P-Glycerate
Ribulose-1:5-di-P
CO_2 Fixation
3-P-Glycerate
2-P-Glycerate
P-enolpyruvate
ACYL-ACP
ACYL-CoA
FATTY ACID
FAT
KETONE BODIES
PYRUVATE
ACETYL-CoA
OXALOACETATE
MALATE
CITRATE
FUMARATE
ISOCITRATE
SUCCINATE
CO_2
SUCCINYL-CoA
2-OXOGLUTARATE
ELECTRON TRANSFER SYSTEM
CHOLESTEROL
HEME
H_2O
Electron Flow from Reduced NAD and Succinate to Oxygen
NADP⁺
NAD⁺
TRYPTOPHAN
TYROSINE
PHENYLALANINE
GLYCINE
SERINE
DNA
RNA
ETHANOL
ACETATE
HISTAMINE
HISTIDINE
CYSTINE
CYSTEINE
METHIONINE
ALANINE
LACTATE
THREONINE
ISOLEUCINE
VALINE
LEUCINE
ASPARTATE
LYSINE
GLUTAMATE
PROLINE
HYDROXYPROLINE
ORNITHINE
ARGININE

reducido → **+ oxidado**

-2 **0** **+2** **+3** **+4**

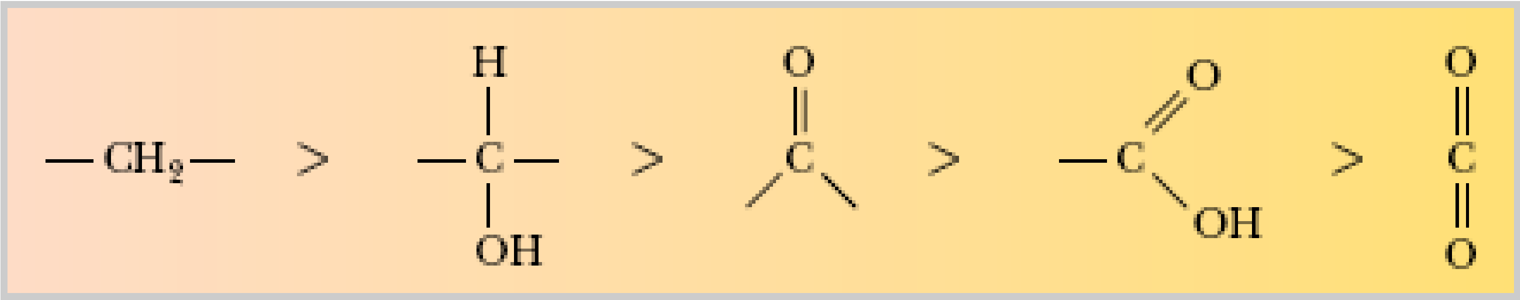
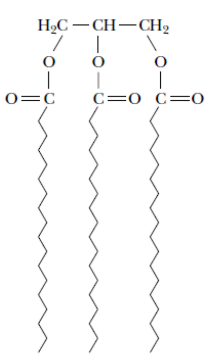
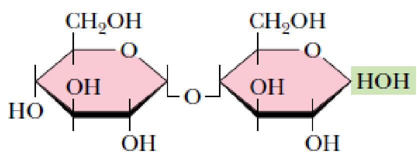
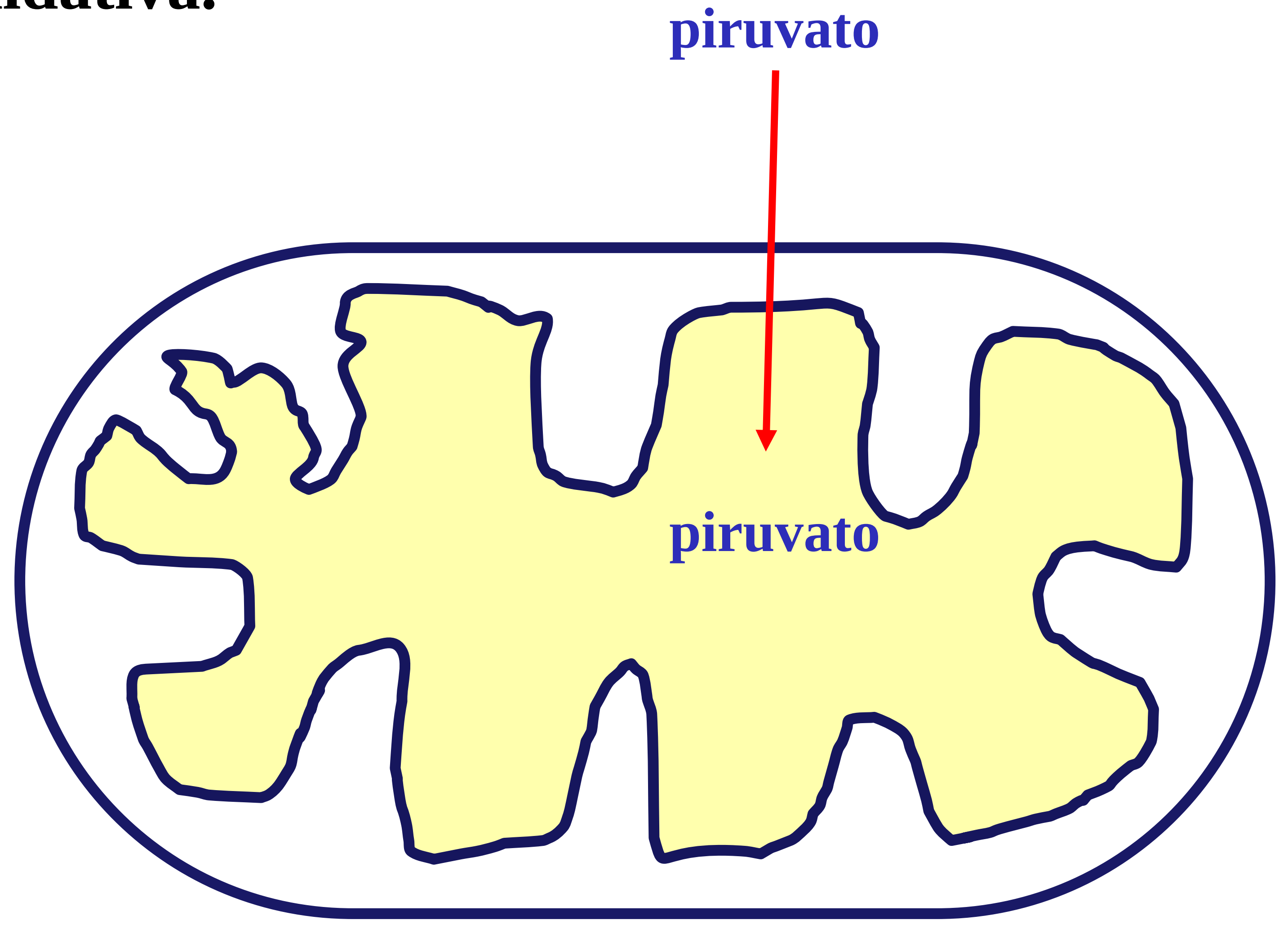


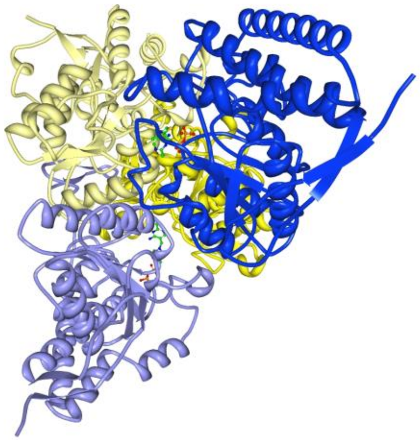
FIGURE 18.9 • Comparison of the state of reduction of carbon atoms in biomolecules: —CH_2— (fats) > —CHOH— (carbohydrates) > —C=O (carbonyls) > —COOH (carboxyls) >CO_2 (carbon dioxide, the final product of catabolism).



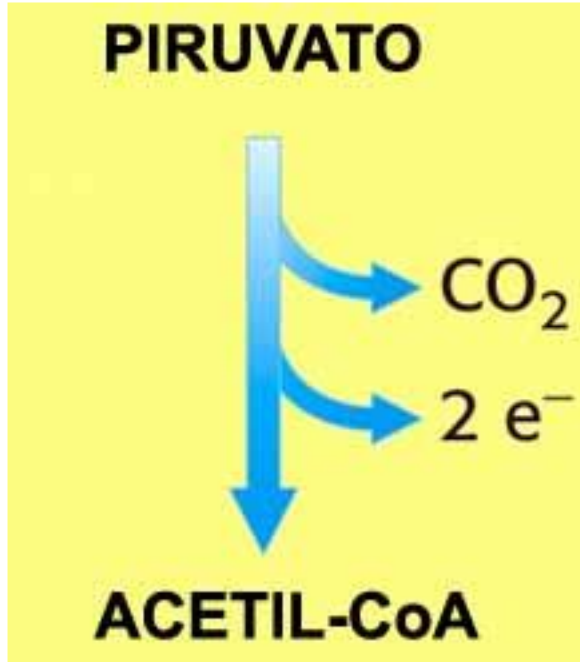


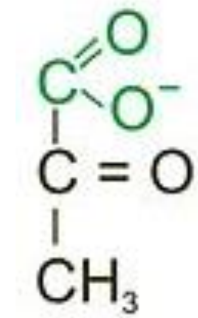
El piruvato formado por la glicolisis en el citoplasma ingresa a la mitocondria en dónde sufre una **descarboxilación oxidativa.**



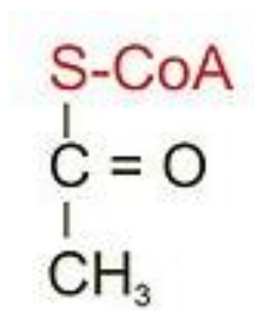


Complejo multienzimático Piruvato Deshidrogenasa

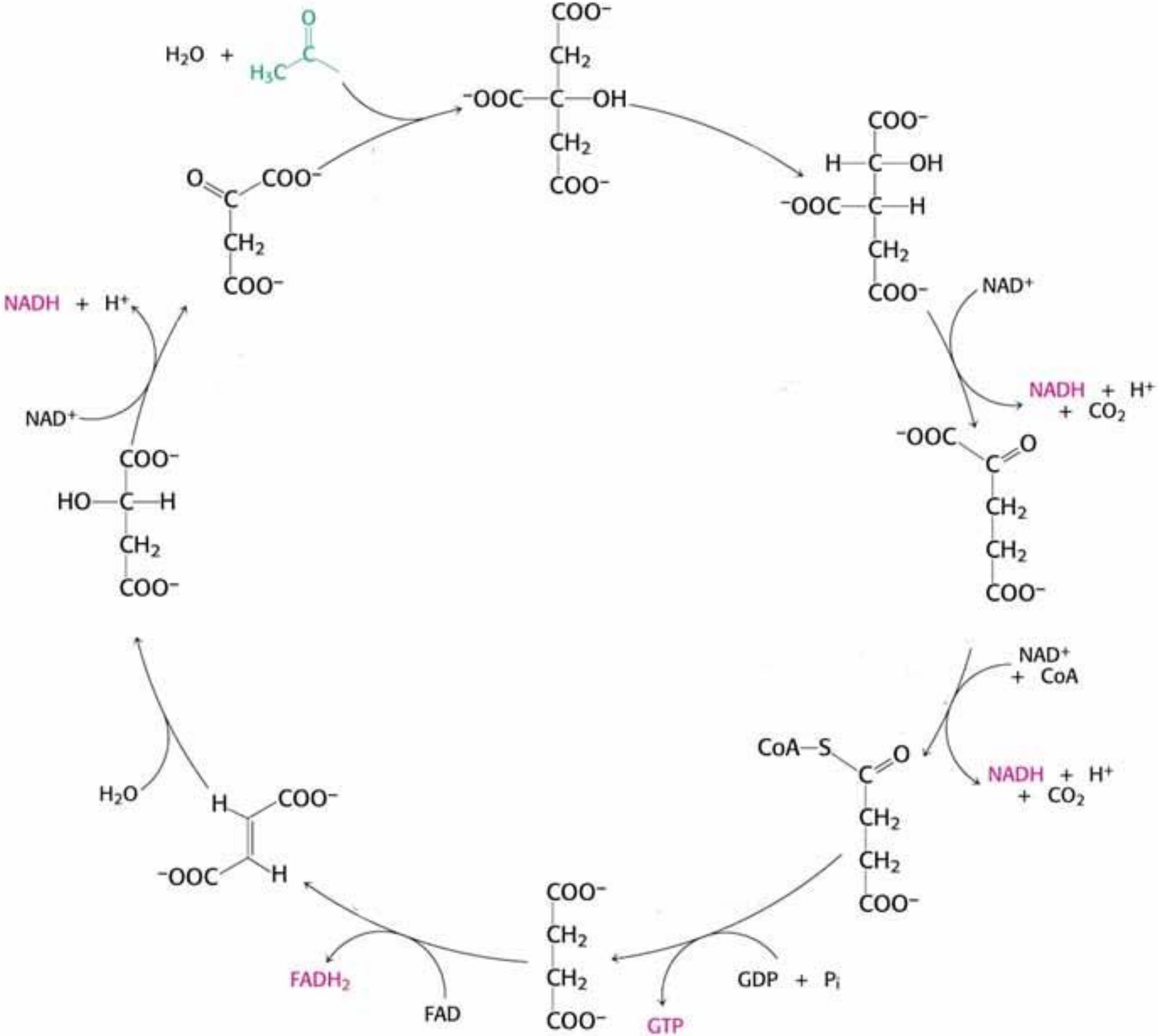




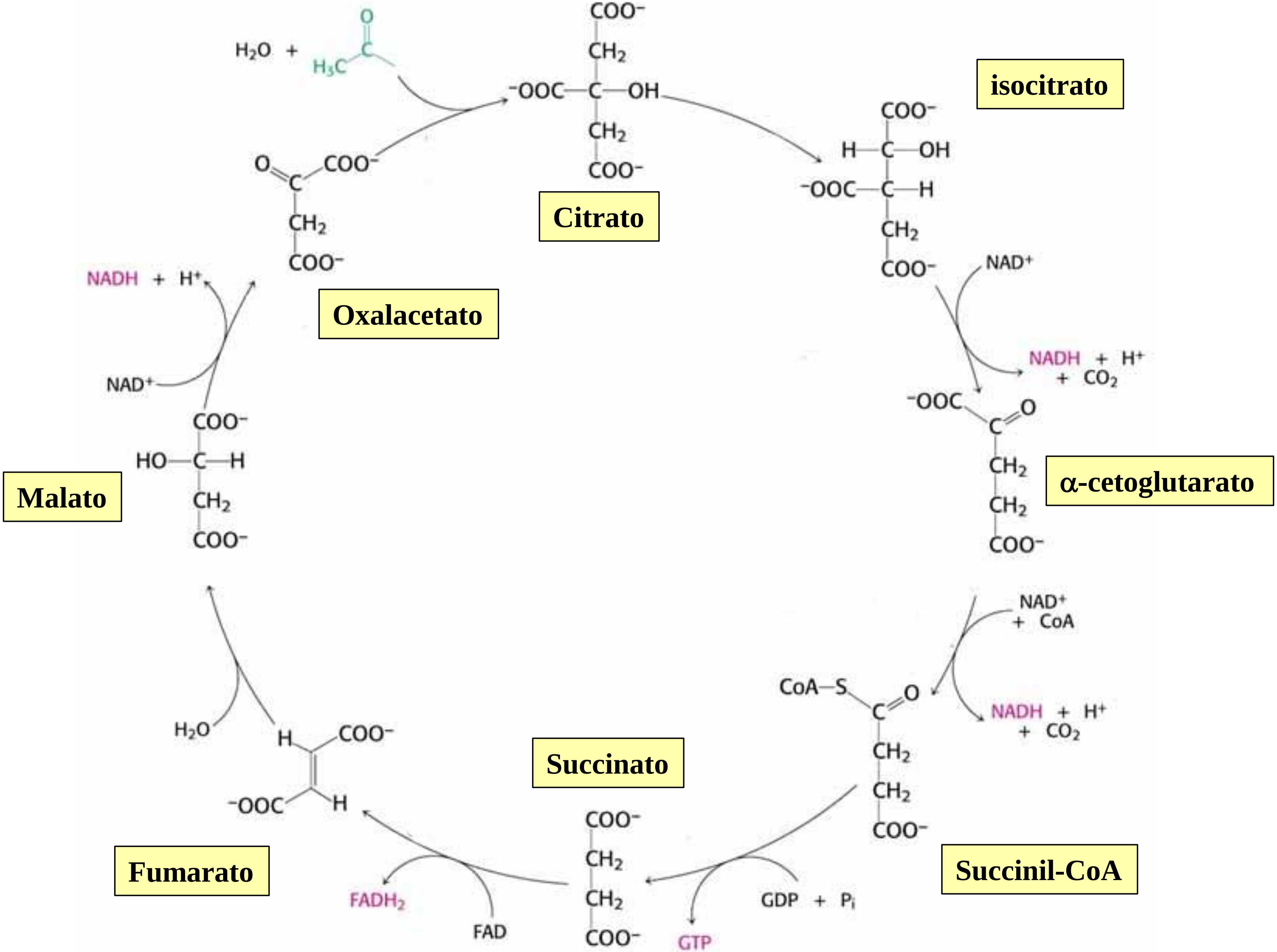
piruvato



acetil-CoA

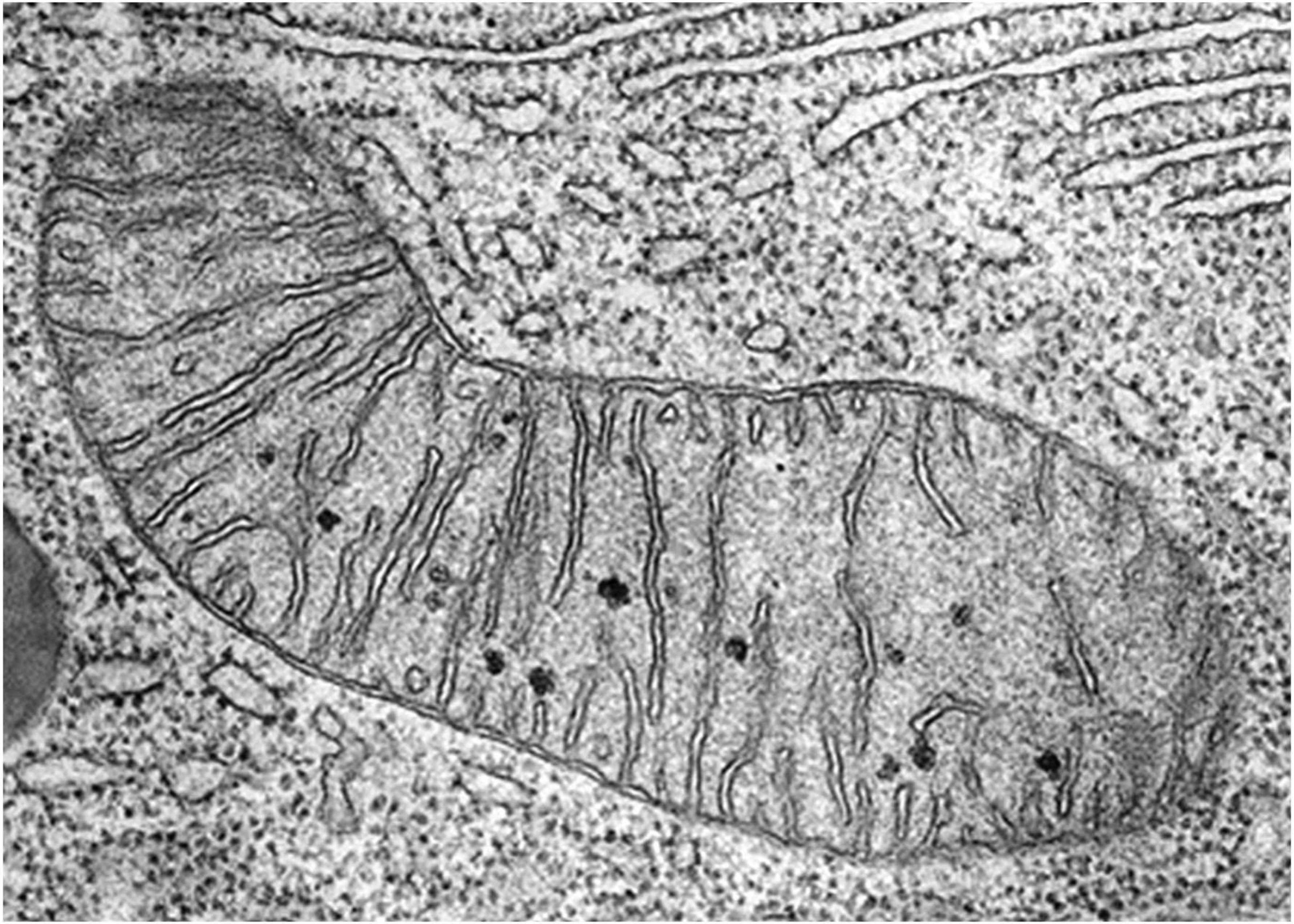


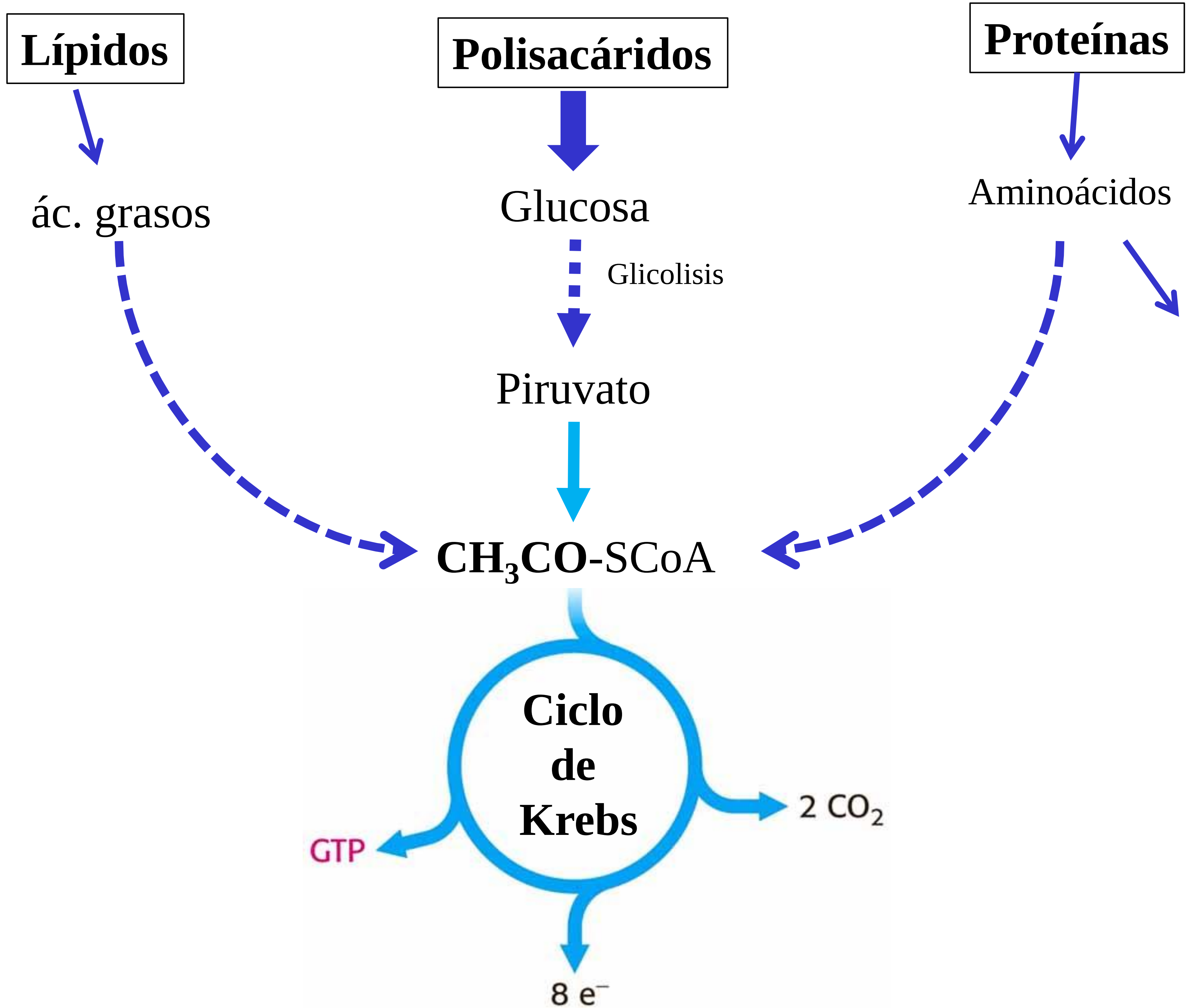
H2O + H3C–C=O
COO−
CH2
−OOC–C–OH
CH2
COO−
H–C–OH
−OOC–C–H
NAD+
NADH + H+ + CO2
NAD+ + CoA
CoA–S
NADH + H+ + CO2
GDP + Pi
GTP
FAD
FADH2
H2O
HO–C–H
NAD+
NADH + H+



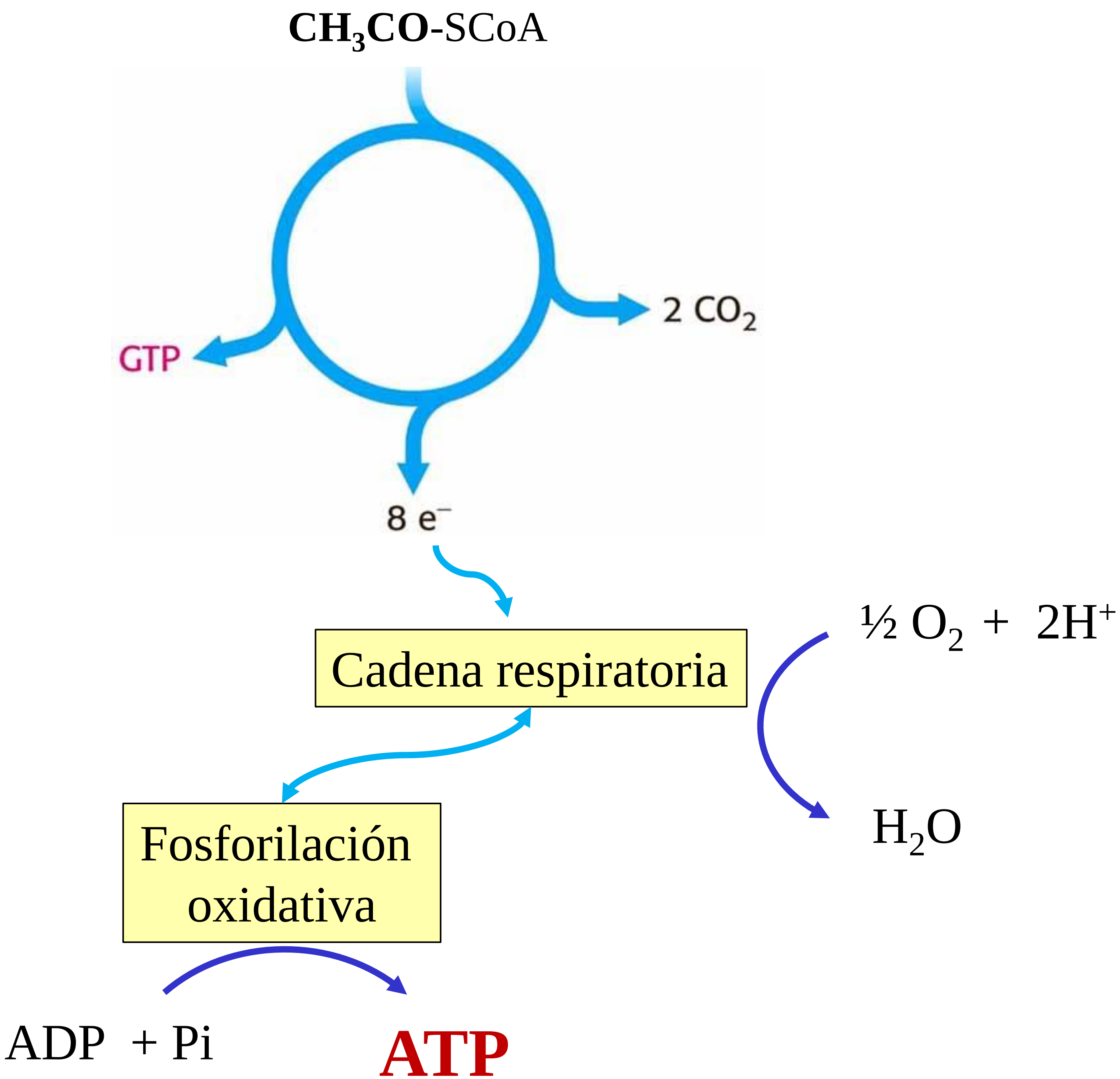
Citrato
isocitrato
α-cetoglutarato
Succinil-CoA
Succinato
Fumarato
Malato
Oxalacetato
H2O +
NAD+
NADH + H+
+ CO2
NAD+
+ CoA
NADH + H+
+ CO2
GDP + Pi
GTP
FAD
FADH2
H2O
NAD+
NADH + H+

Hans Krebs, en 1937 propuso la existencia del ciclo del ácido cítrico basado en varios descubrimientos previos.





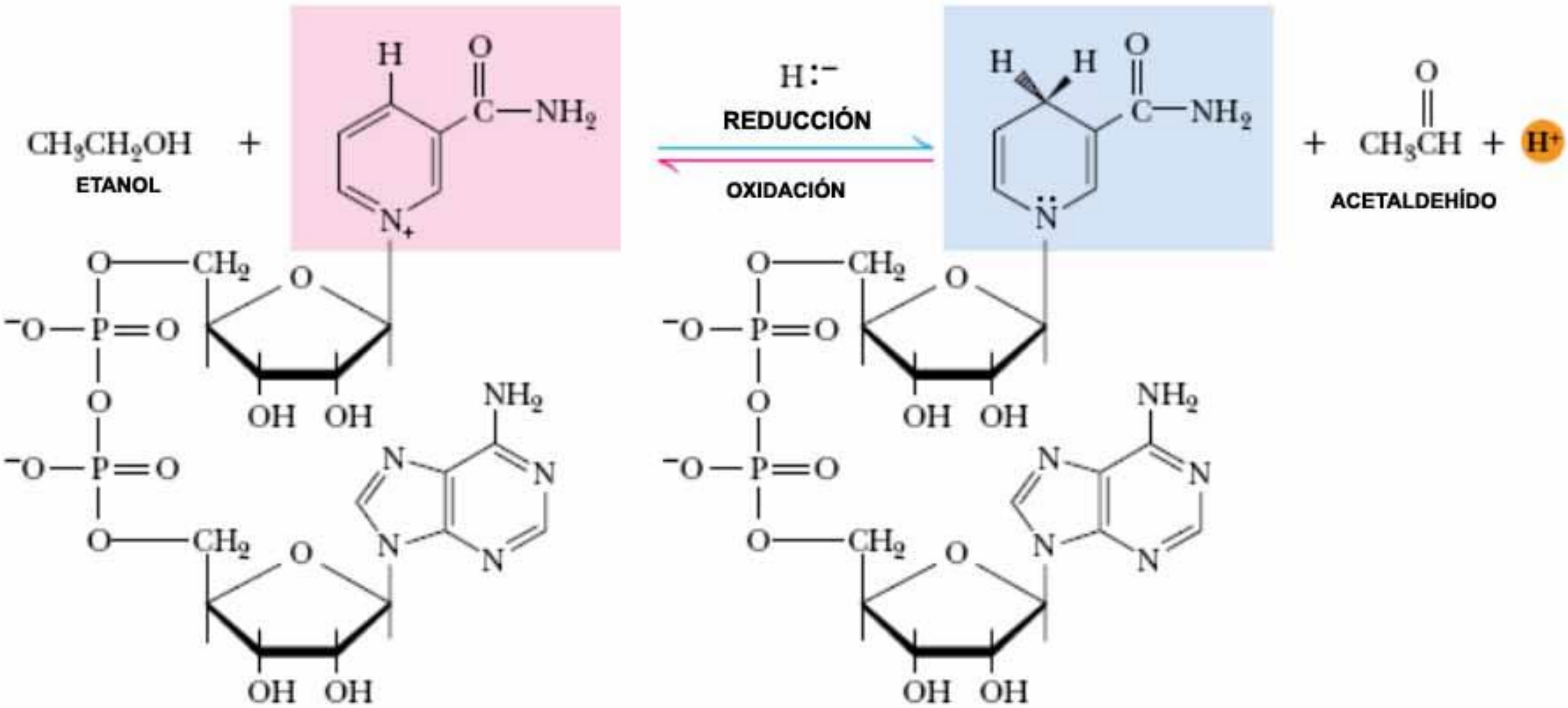
Lípidos
Polisacáridos
Proteínas
ác. grasos
Glucosa
Aminoácidos
Glicolisis
Piruvato
CH_3CO-SCoA
Ciclo de Krebs
GTP
2 CO_2
8 e^-


CH_3CO-SCoA
GTP
$2\ CO_2$
$8\ e^-$
Cadena respiratoria
$\frac{1}{2}\ O_2\ +\ 2H^+$
H_2O
Fosforilación oxidativa
ADP + Pi
ATP

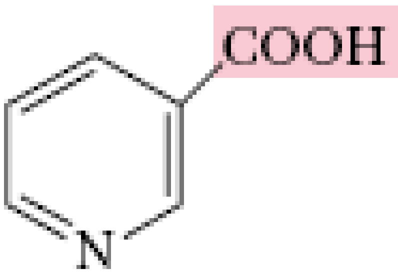
Cofactores reducidos:

NADH

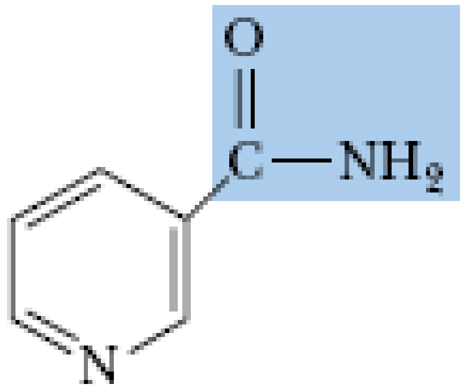
$FADH_2$


CH3CH2OH
ETANOL
H:⁻
REDUCCIÓN
OXIDACIÓN
ACETALDEHÍDO
CH3CH
H⁺

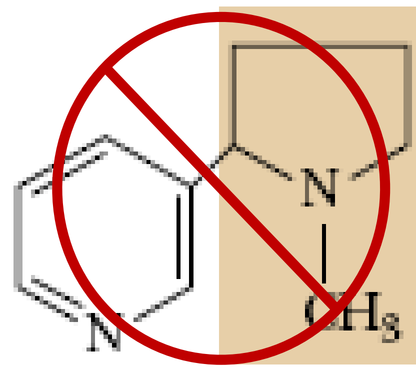
NAD$^+$ NADH



Nicotinic acid



Nicotinamide

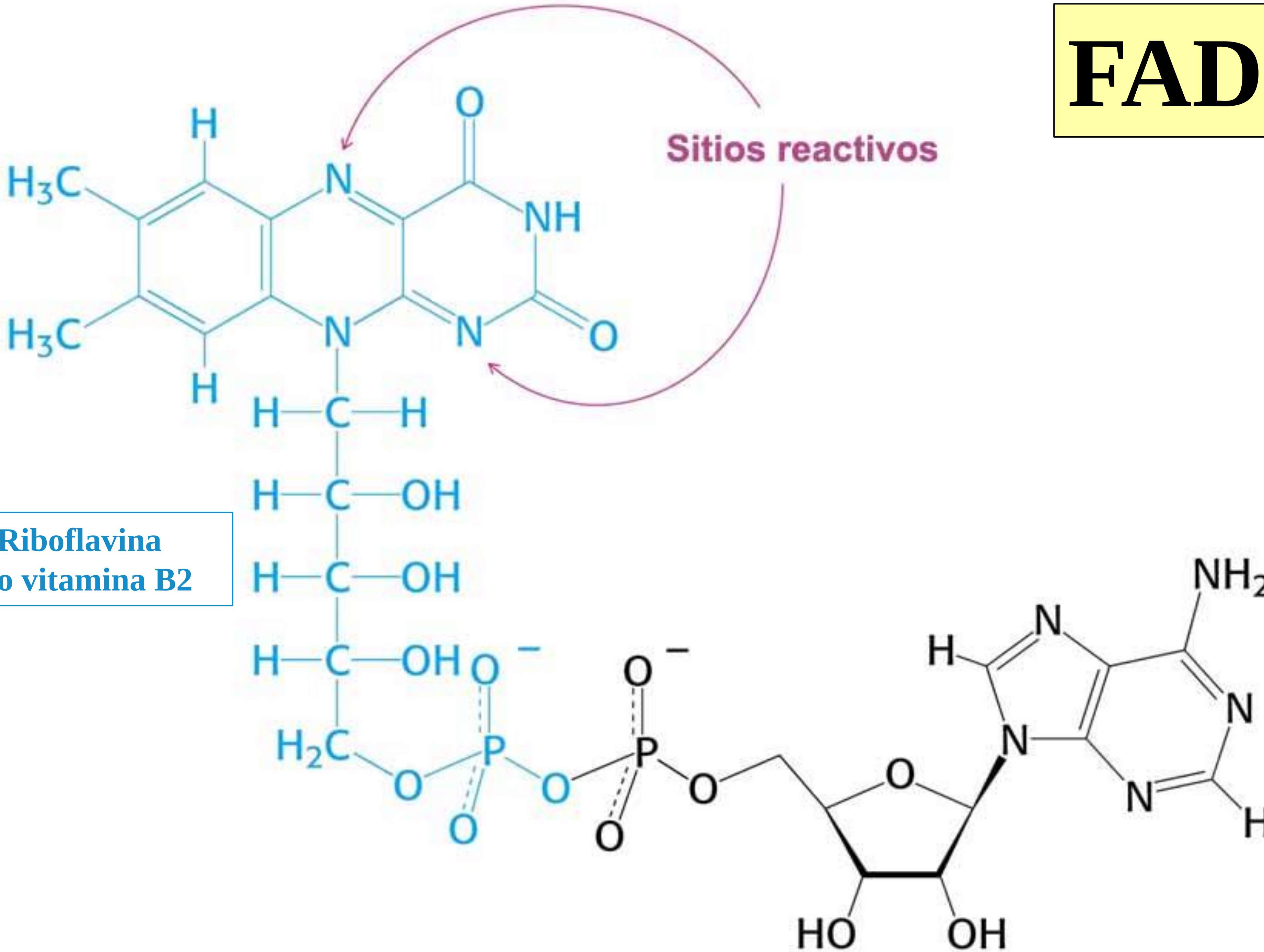


Nicotine

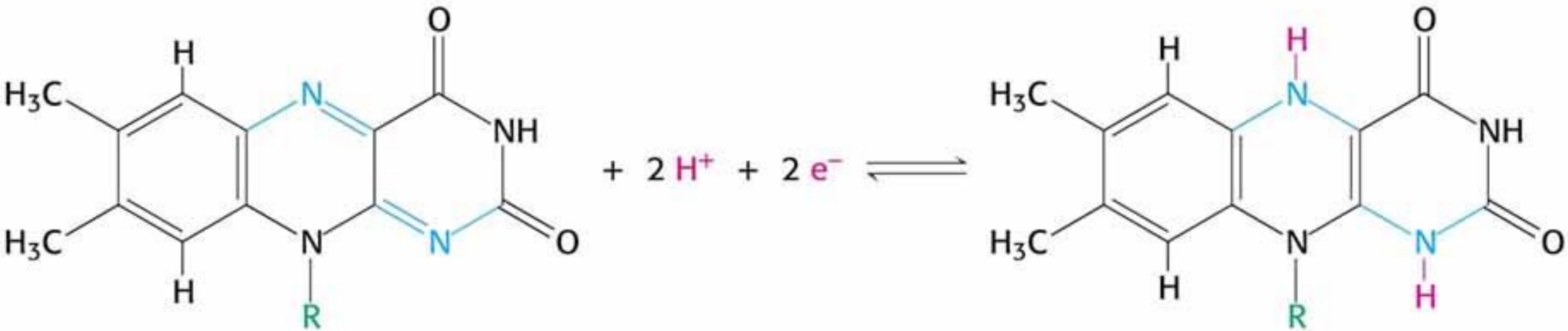
Niacina
Vitamina B3

Alcaloide presente
en el tabaco

FAD



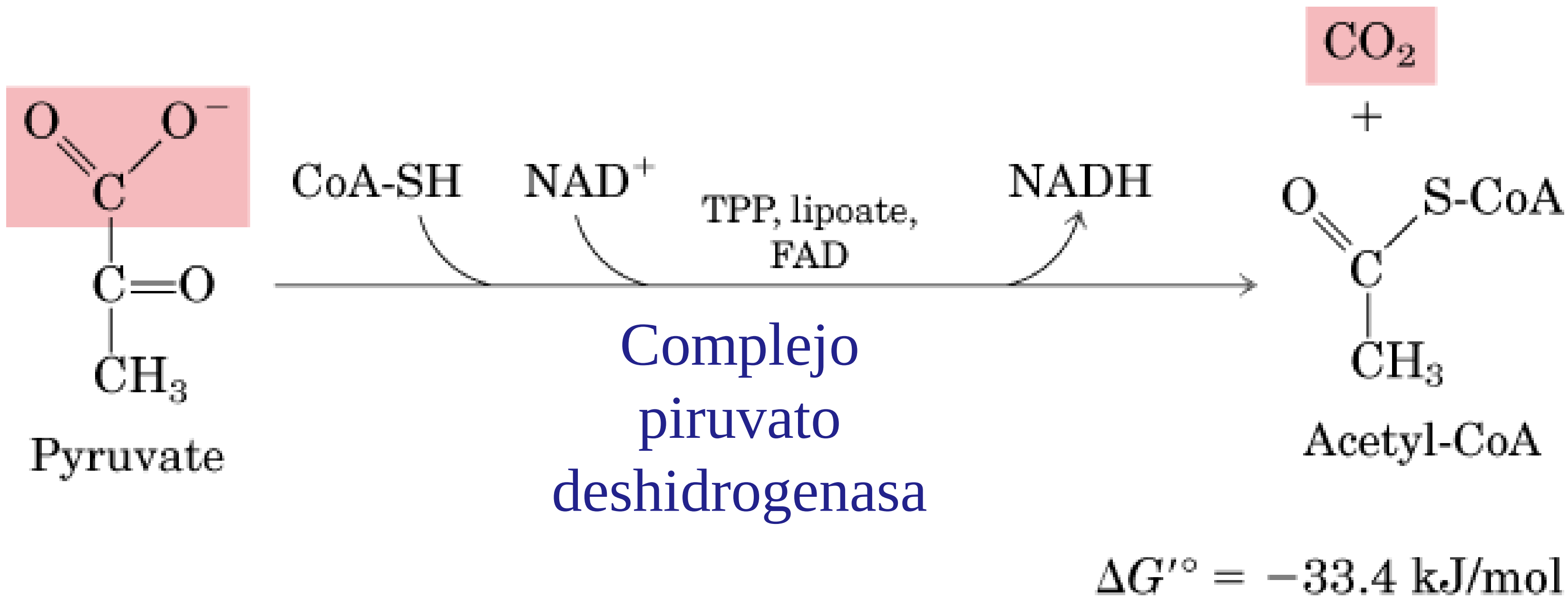
Riboflavina
o vitamina B2



Forma oxidada
(FAD)

Forma reducida
($FADH_2$)

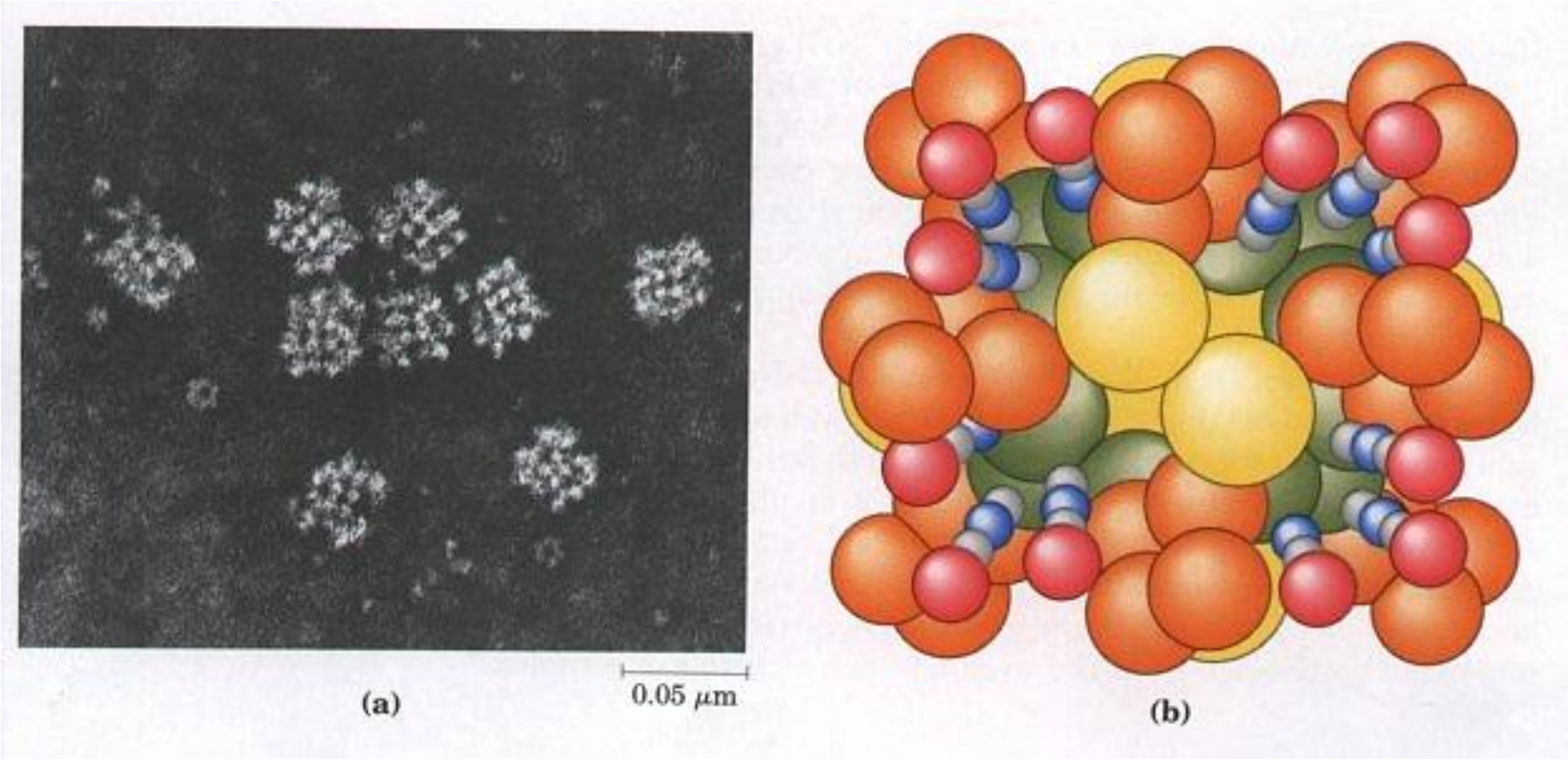
Complejo multienzimático
PIRUVATO DESHIDROGENASA

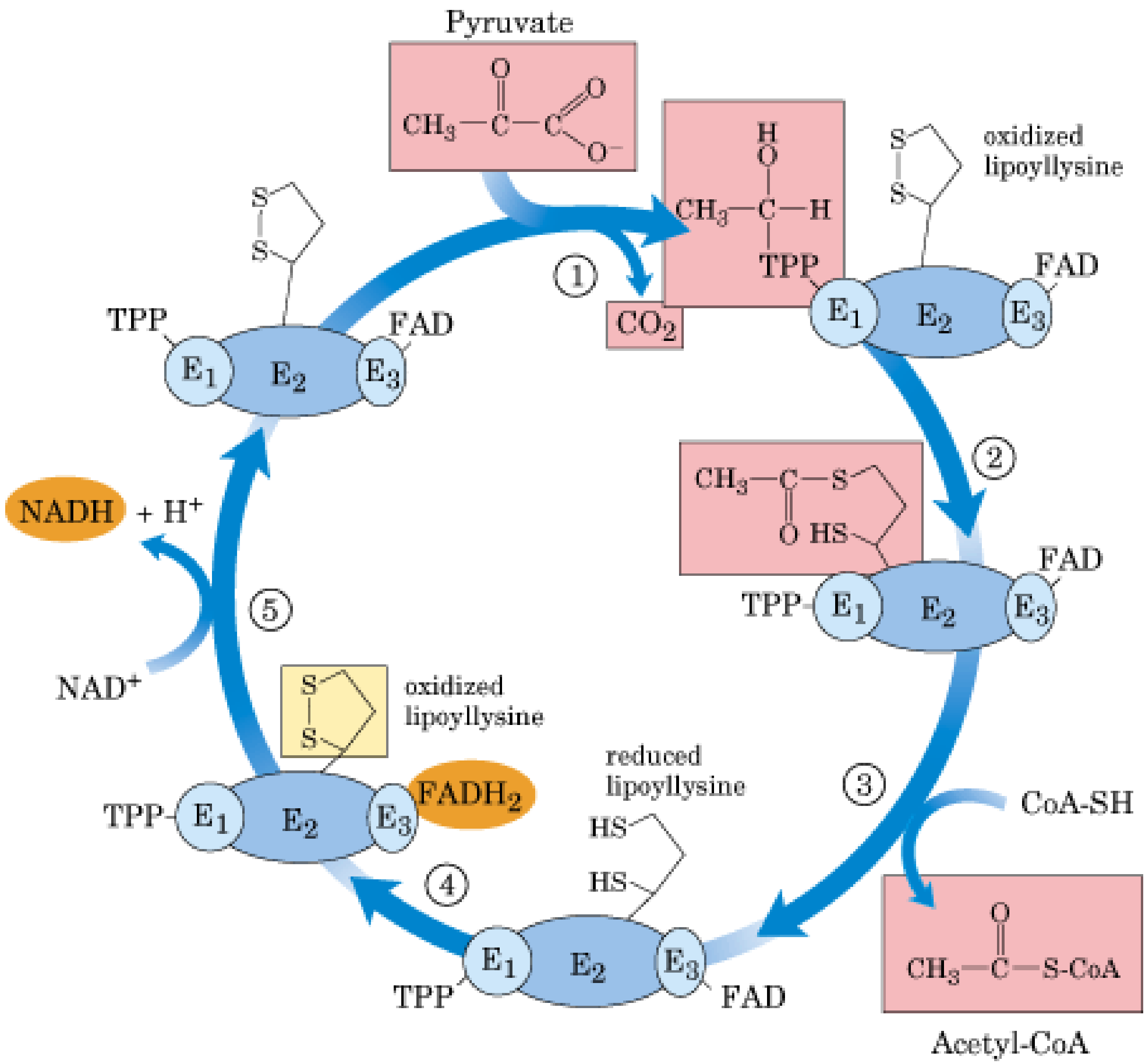


Complejo
piruvato
deshidrogenasa

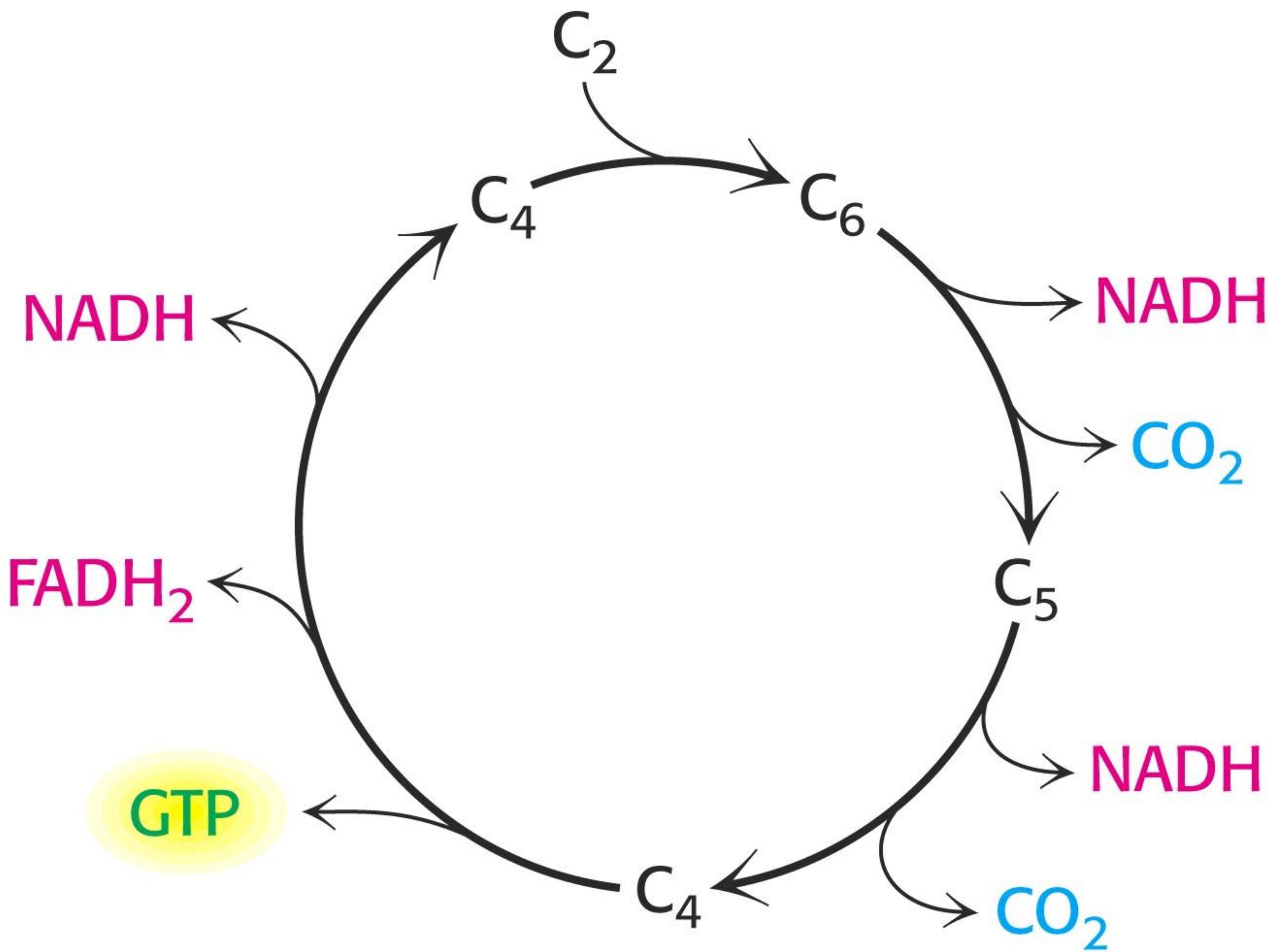
Piruvato Deshidrogenasa:

un complejo multienzimático

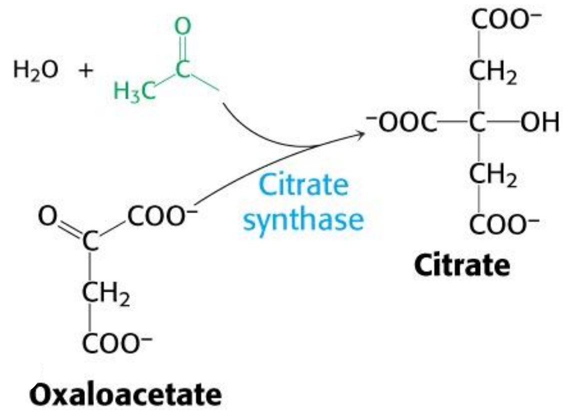


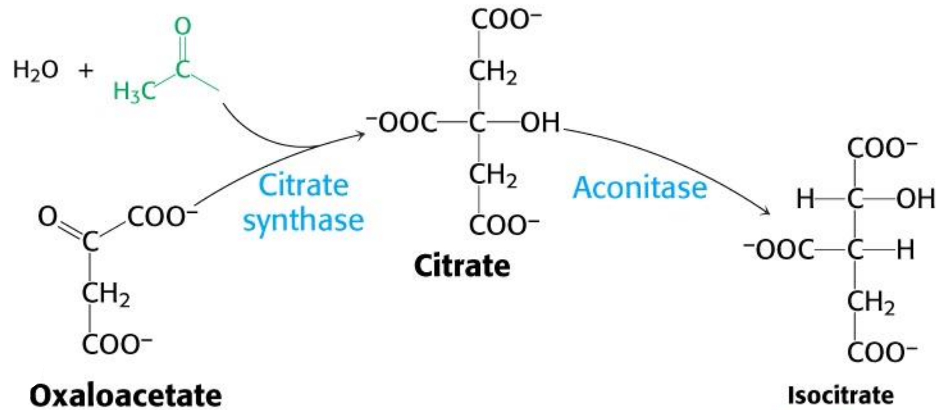


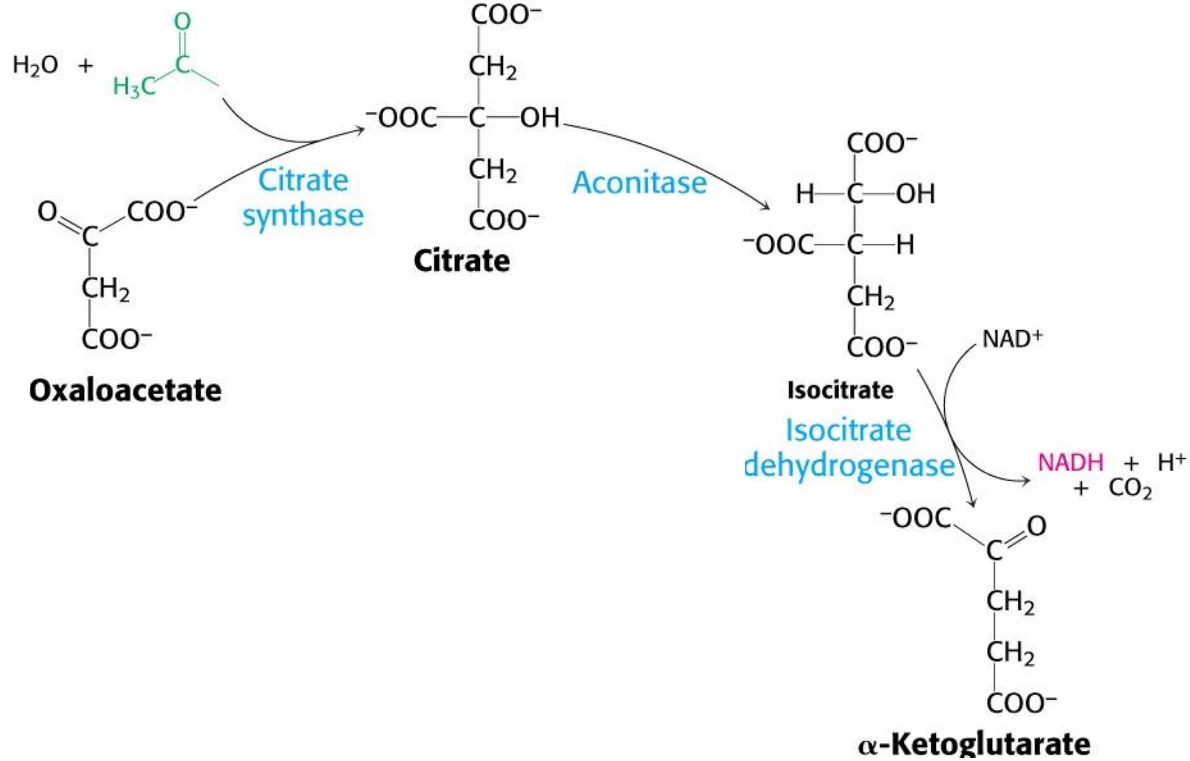
Pyruvate
$CH_3-C(=O)-C(=O)O^-$
$CH_3-C(OH)(H)-TPP$
CO_2
oxidized lipoyllysine
FAD
E_1
E_2
E_3
TPP
$CH_3-C(=O)-S$ HS
CoA-SH
Acetyl-CoA
$CH_3-C(=O)-S\text{-}CoA$
reduced lipoyllysine
HS
HS
$FADH_2$
NAD^+
NADH
$+ H^+$
1
2
3
4
5



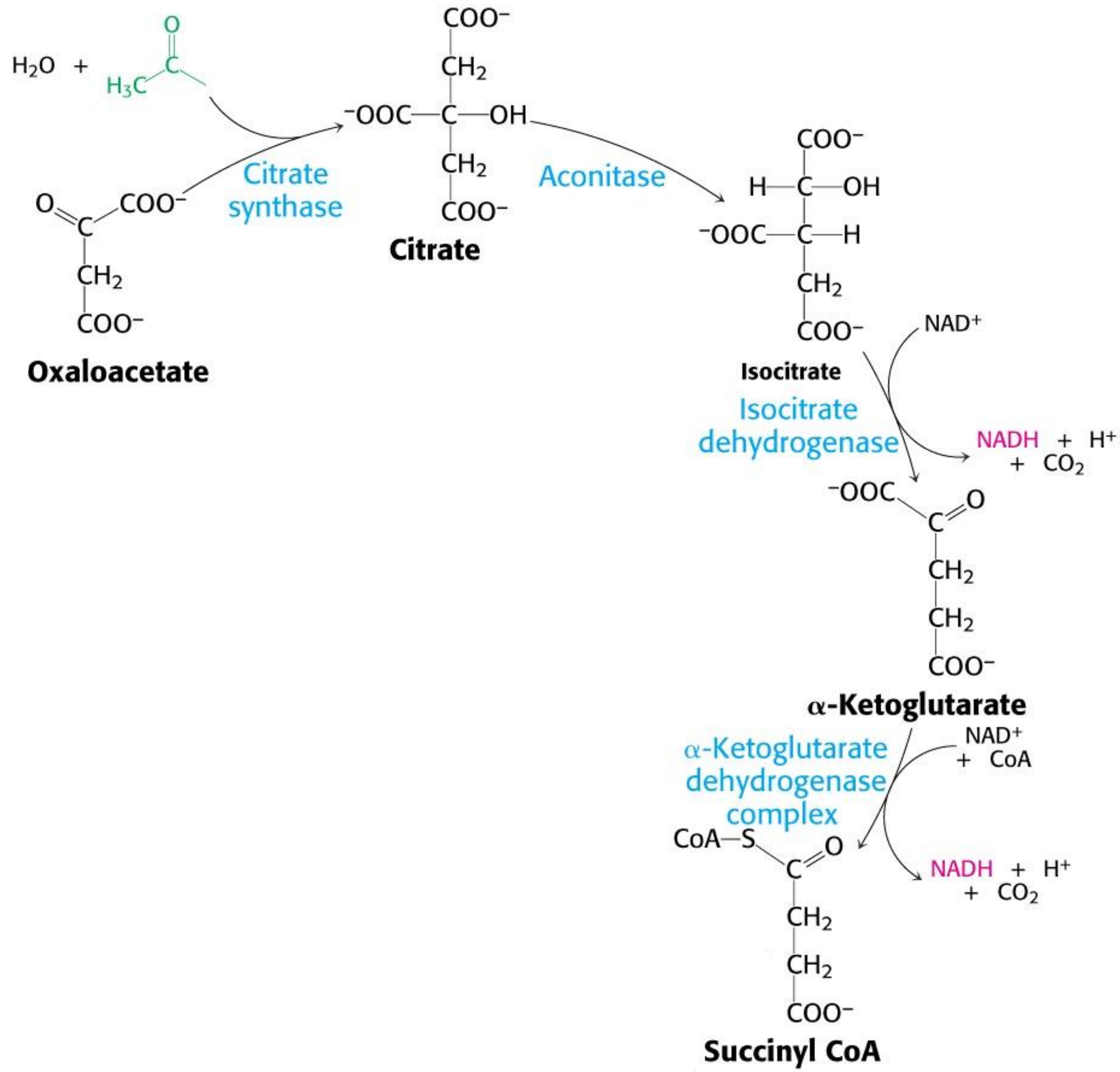
C2
C4
C6
NADH
CO2
C5
NADH
CO2
C4
GTP
FADH2
NADH


H2O +
Citrate
synthase
Oxaloacetate
Citrate

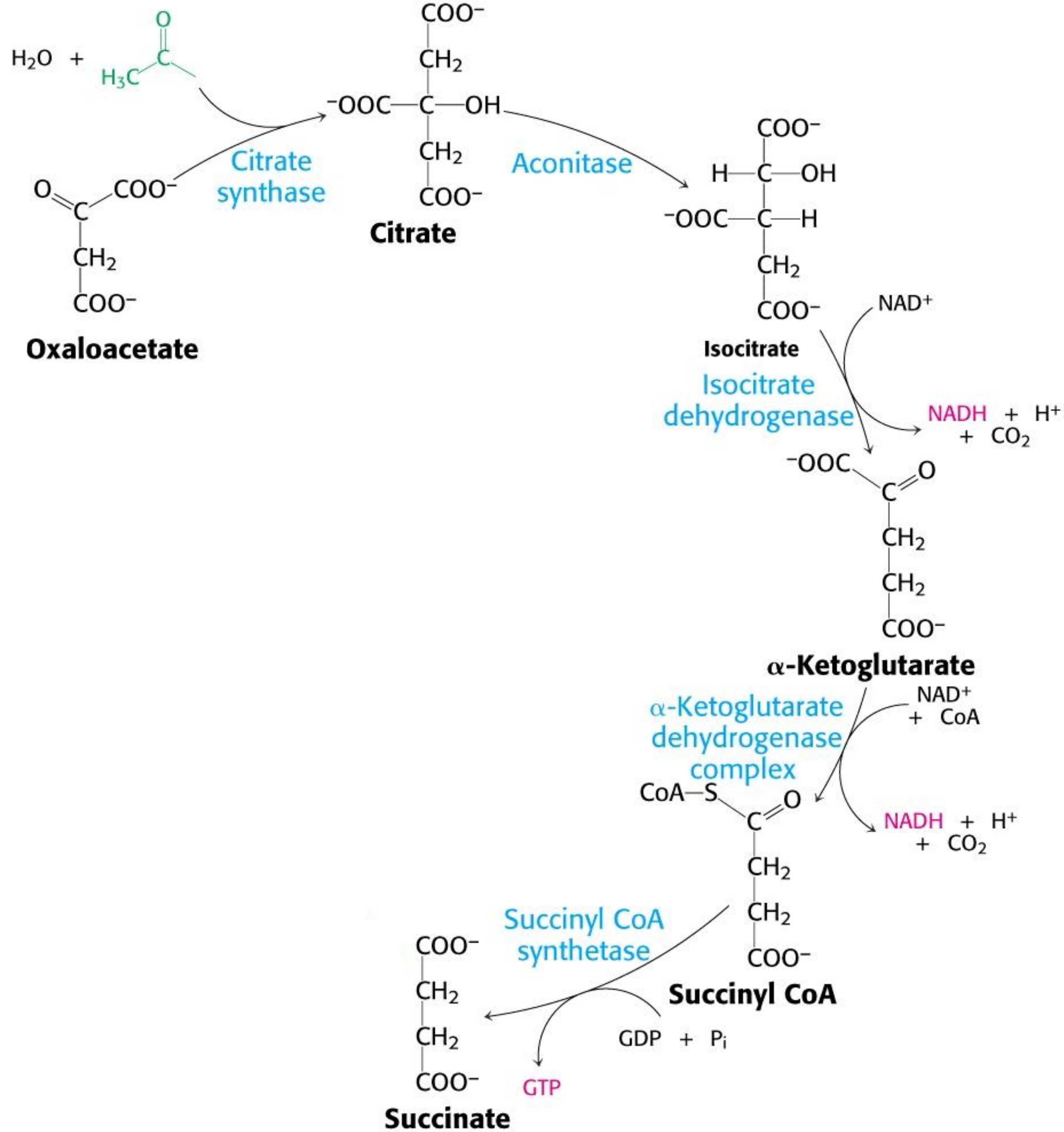

H_2O +
Citrate synthase
Aconitase
Oxaloacetate
Citrate
Isocitrate

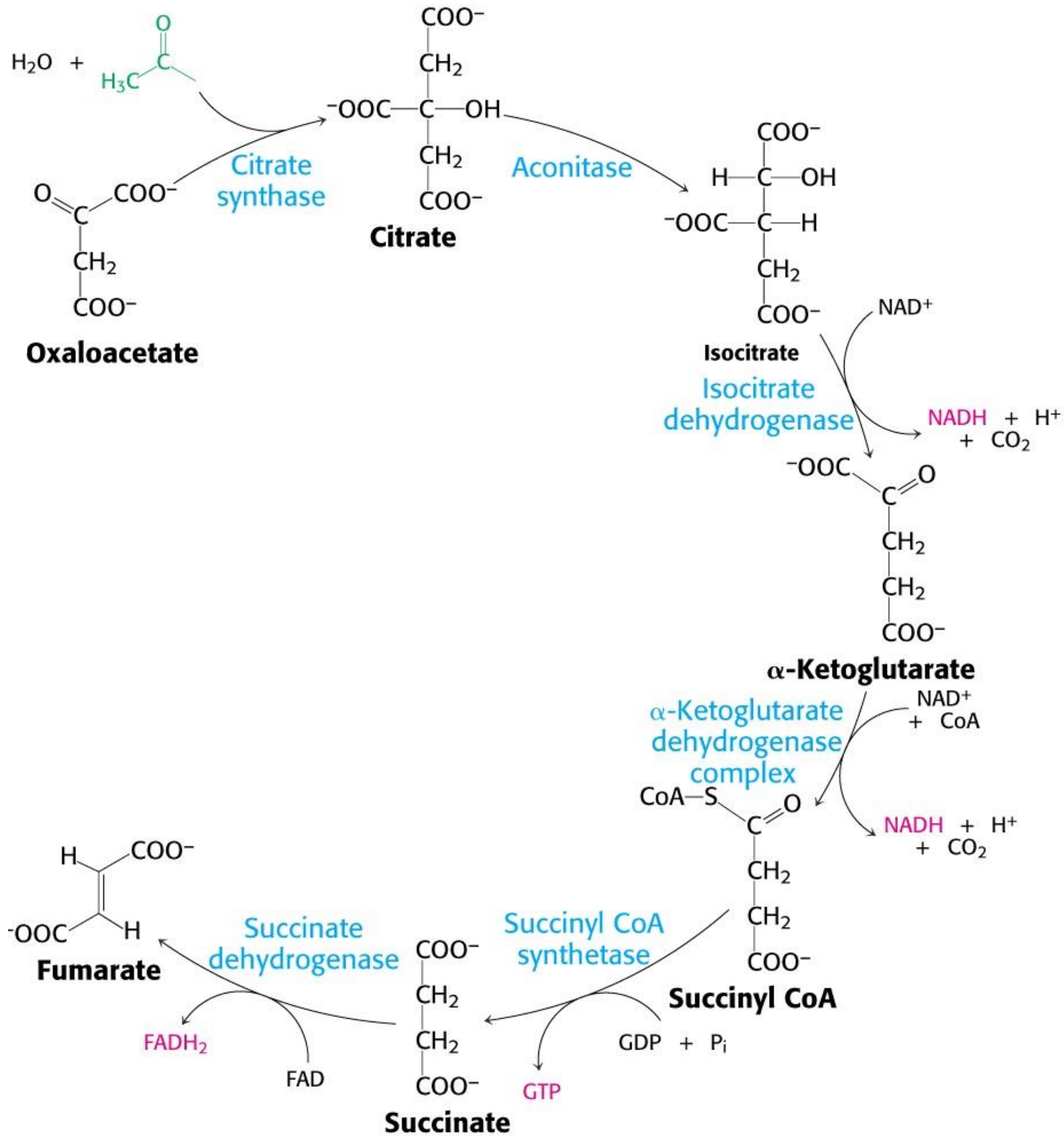


H2O +
Citrate synthase
Citrate
Aconitase
Oxaloacetate
Isocitrate
NAD+
Isocitrate dehydrogenase
NADH + H+
+ CO2
α-Ketoglutarate



H2O +
Citrate synthase
Oxaloacetate
Citrate
Aconitase
Isocitrate
NAD+
Isocitrate dehydrogenase
NADH + H+ + CO2
α-Ketoglutarate
NAD+ + CoA
α-Ketoglutarate dehydrogenase complex
NADH + H+ + CO2
Succinyl CoA


H2O +
Citrate synthase
Citrate
Aconitase
Oxaloacetate
Isocitrate
NAD+
Isocitrate dehydrogenase
NADH + H+ + CO2
α-Ketoglutarate
NAD+ + CoA
α-Ketoglutarate dehydrogenase complex
NADH + H+ + CO2
Succinyl CoA
Succinyl CoA synthetase
GDP + Pi
GTP
Succinate



H2O +
Citrate synthase
Citrate
Aconitase
Isocitrate
Oxaloacetate
NAD+
Isocitrate dehydrogenase
NADH + H+ + CO2
α-Ketoglutarate
NAD+ + CoA
α-Ketoglutarate dehydrogenase complex
NADH + H+ + CO2
Succinyl CoA
Succinyl CoA synthetase
GDP + Pi
GTP
Succinate
Succinate dehydrogenase
FAD
FADH2
Fumarate

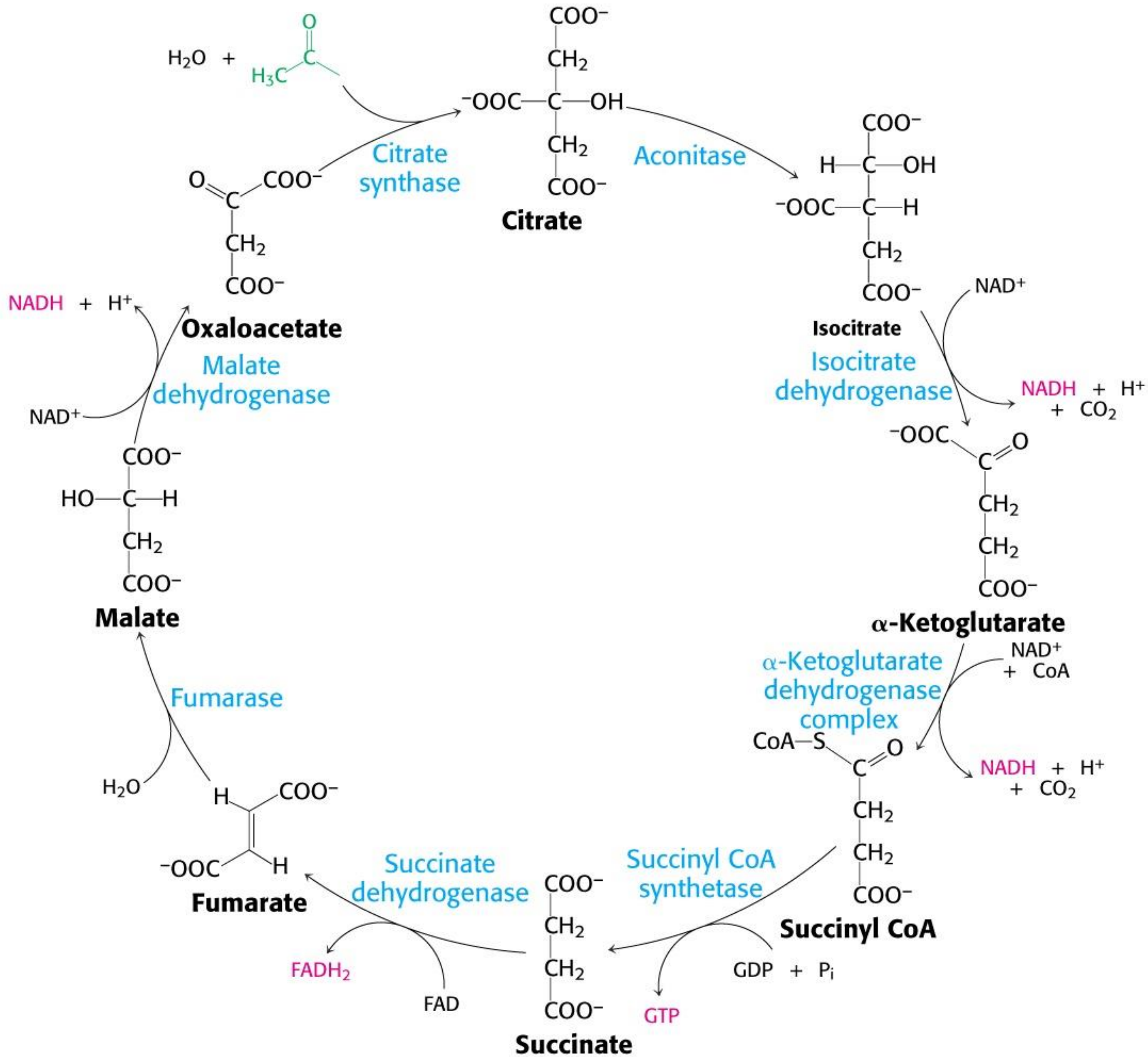

H2O +
Citrate synthase
Citrate
Aconitase
Isocitrate
NAD+
Isocitrate dehydrogenase
NADH + H+ + CO2
α-Ketoglutarate
NAD+ + CoA
α-Ketoglutarate dehydrogenase complex
NADH + H+ + CO2
Succinyl CoA
Succinyl CoA synthetase
GDP + Pi
GTP
Succinate
Succinate dehydrogenase
FAD
FADH2
Fumarate
Fumarase
H2O
Malate
NAD+
Malate dehydrogenase
NADH + H+
Oxaloacetate

TABLE 17.2 **Citric acid cycle**

Step	Reaction	Enzyme	Prosthetic group	Type*	$\Delta G^{\circ\prime}$ kcal mol^{-1}	$\Delta G^{\circ\prime}$ kJ mol^{-1}
1	Acetyl CoA + oxaloacetate + $H_2O \longrightarrow$ citrate + CoA + H^+	Citrate synthase		a	−7.5	−31.4
2a	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe–S	b	+2.0	+8.4
2b	*cis*-Aconitate + $H_2O \rightleftharpoons$ isocitrate	Aconitase	Fe–S	c	−0.5	−2.1
3	Isocitrate + $NAD^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e	−2.0	−8.4
4	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e	−7.2	−30.1
5	Succinyl CoA + P_i + GDP $\rightleftharpoons$ succinate + GTP + CoA	Succinyl CoA synthetase		f	−0.8	−3.3
6	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$ (enzyme-bound)	Succinate dehydrogenase	FAD, Fe–S	e	~0	0
7	Fumarate + $H_2O \rightleftharpoons$ L-malate	Fumarase		c	−0.9	−3.8
8	L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e	+7.1	+29.7

*Reaction type: (a) condensation; (b) dehydration; (c) hydration; (d) decarboxylation; (e) oxidation; (f) substrate-level phosphorylation.

Reacción Global del Ciclo de Krebs

$$\text{Acetil-CoA} + 3NAD^+ + FAD + GDP + P_i + 2H_2O$$

$$\downarrow$$

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

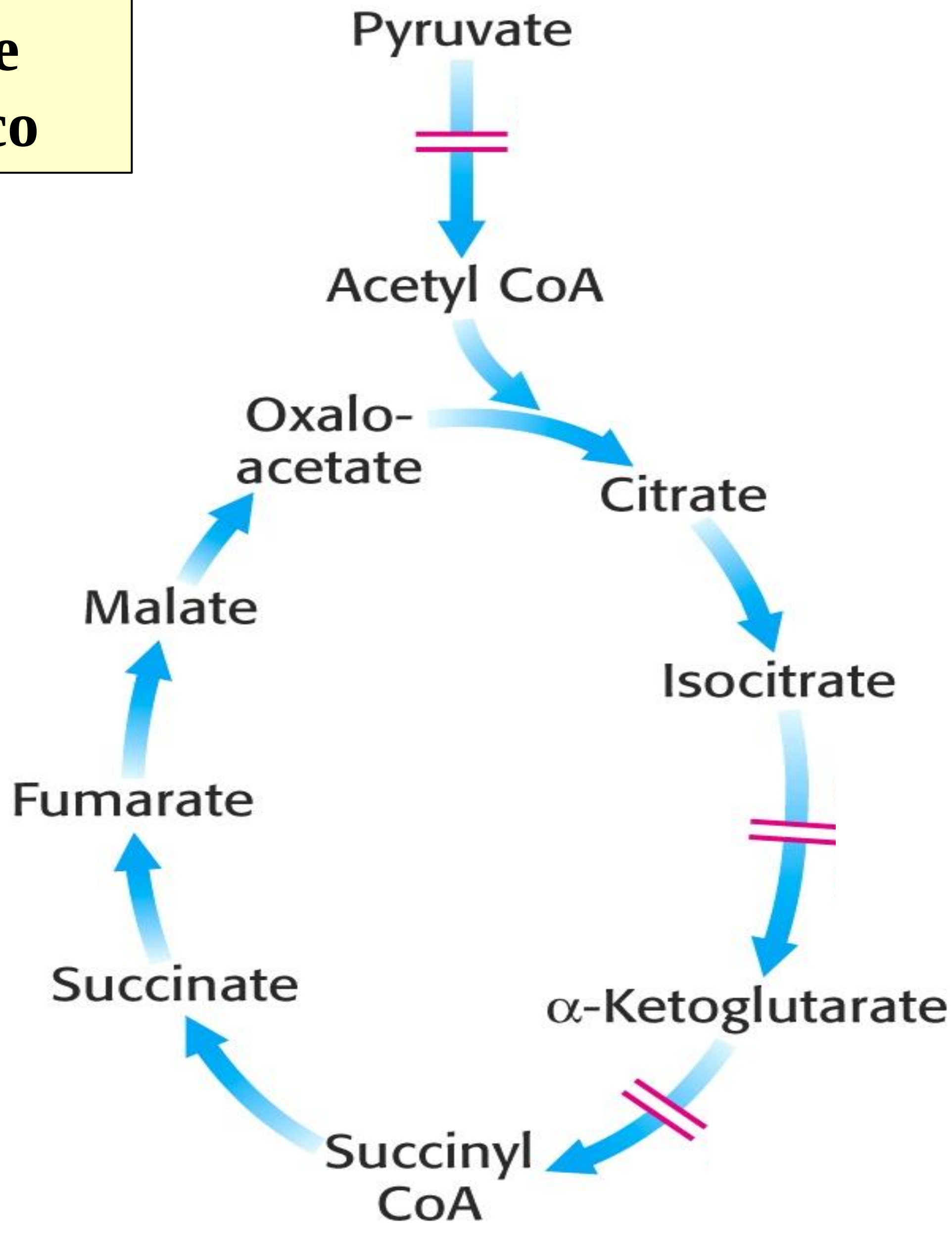
Regulación del Ciclo de Krebs

La velocidad del C.K. debe ajustarse de acuerdo a las necesidades de ATP de la célula

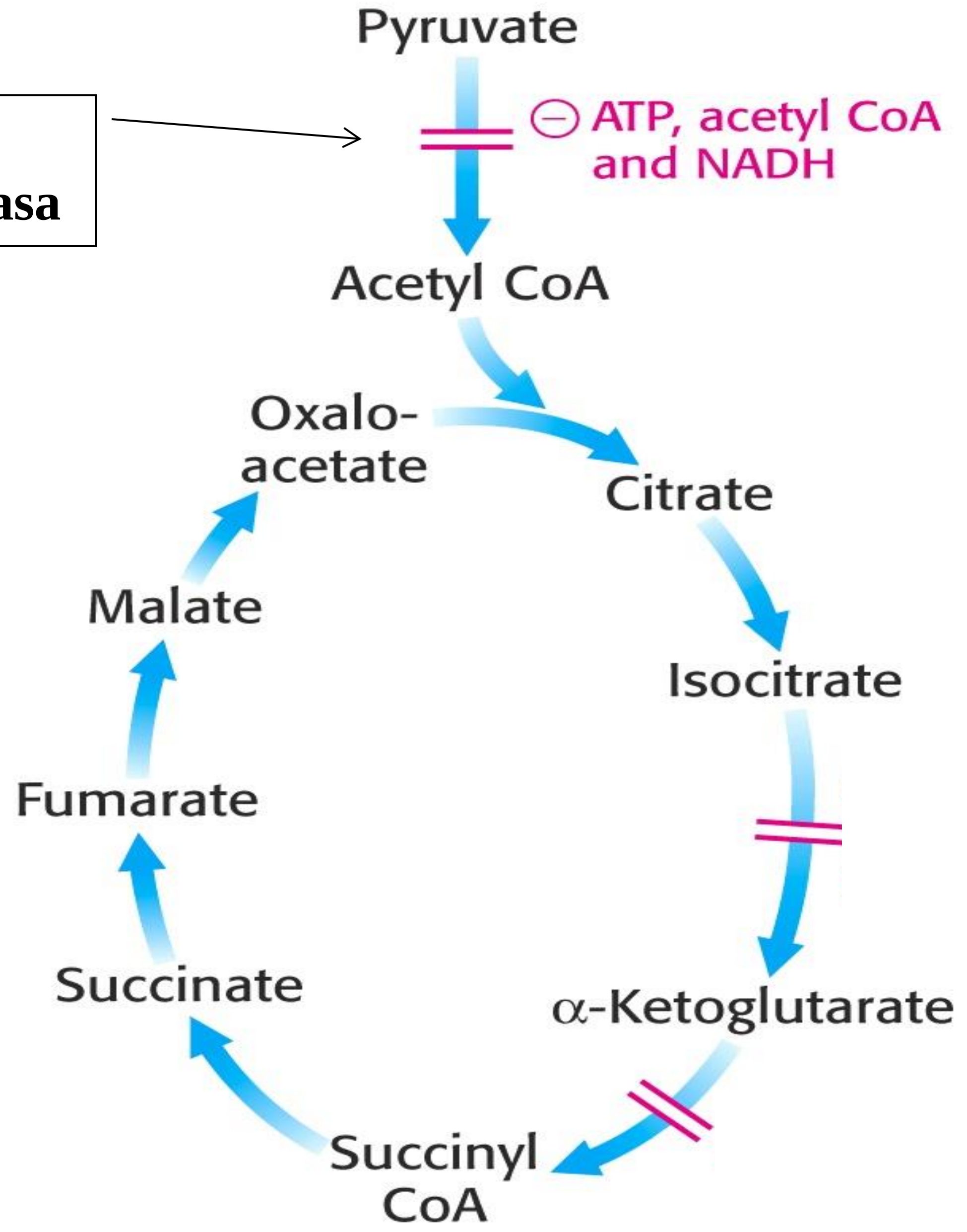
Relación de concentraciones en condición:

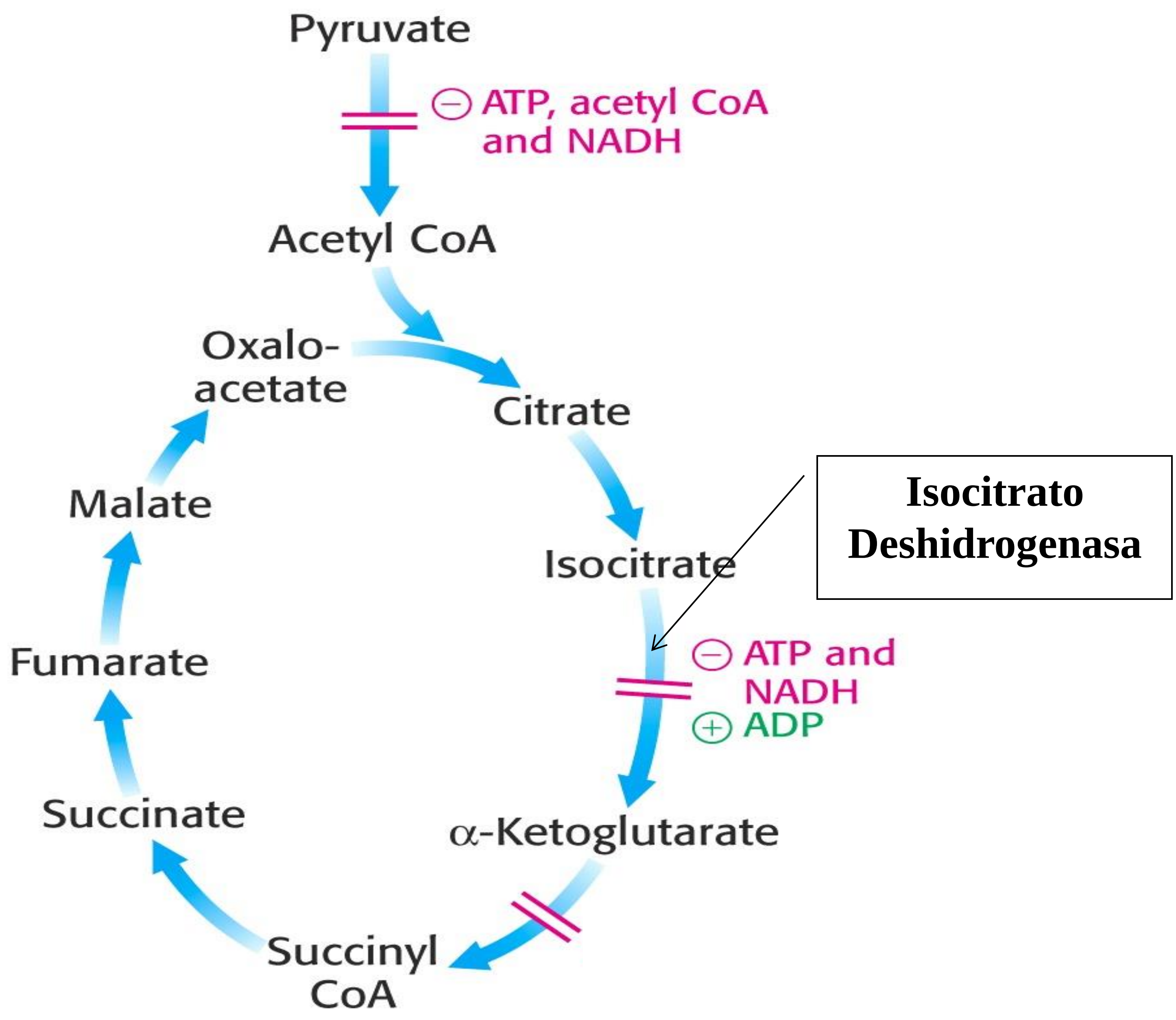
	En reposo	Alta actividad
$\frac{[NAD^+]}{[NADH]}$	Baja $[NAD^+]$	Alta $[NAD^+]$
$\frac{[FAD]}{[FADH_2]}$	Baja [FAD]	Alta [FAD]
$\frac{[ADP]}{[ATP]}$	Baja [ADP]	Alta [ADP]
	El CK se inhibe	**El CK se activa**

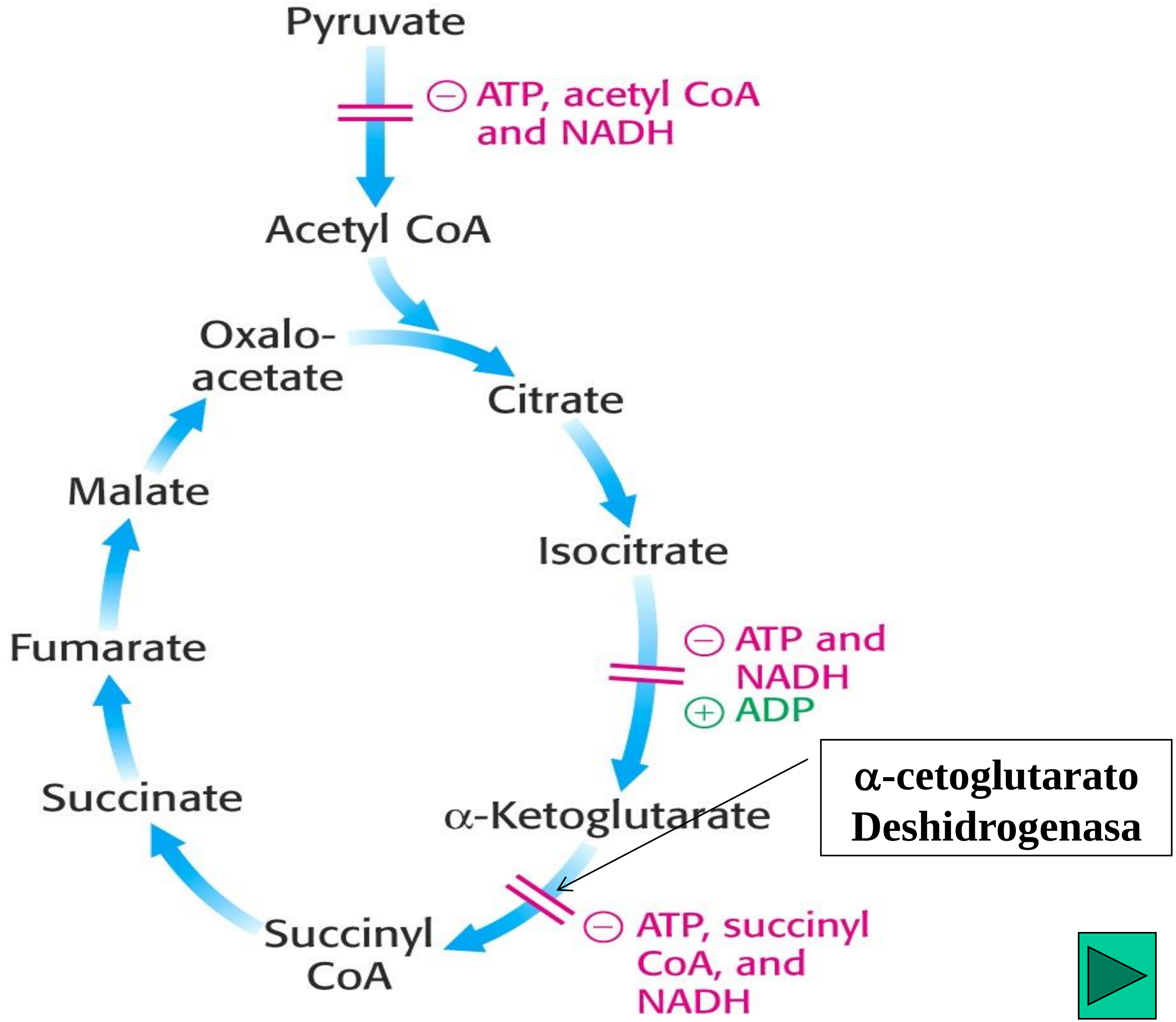
Puntos de regulación de tipo alostérico

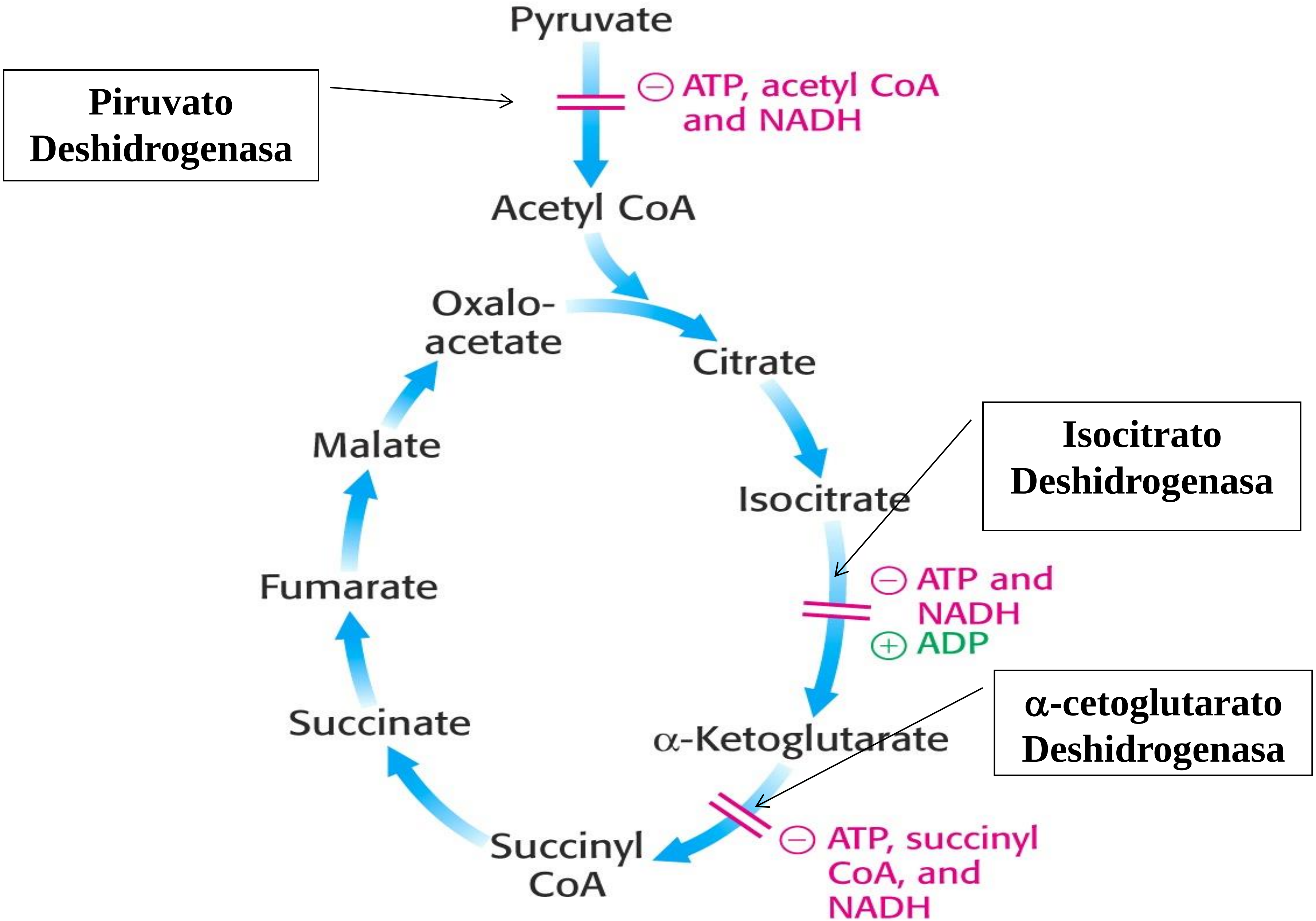


Piruvato Deshidrogenasa



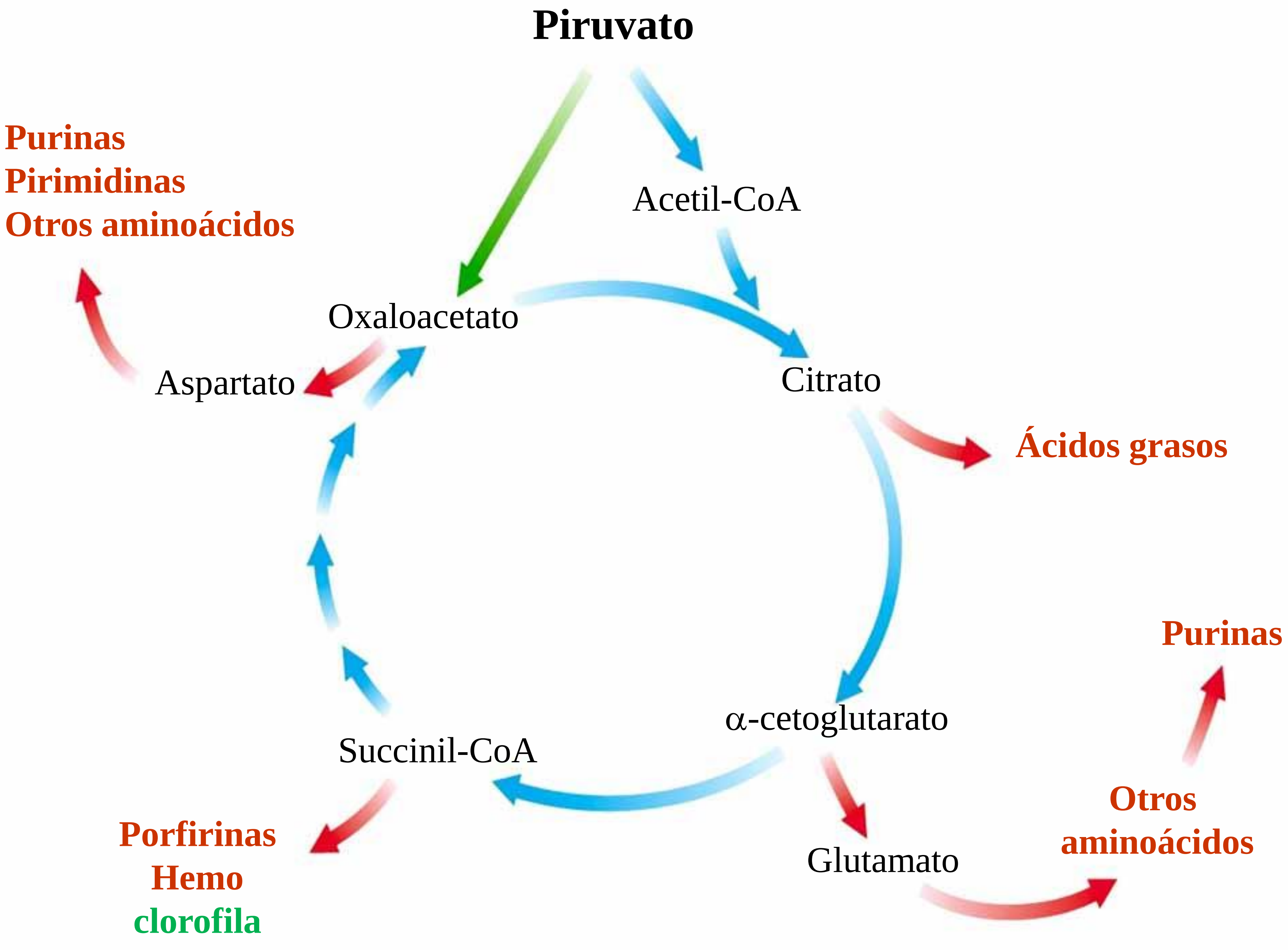

Pyruvate
⊖ ATP, acetyl CoA and NADH
Acetyl CoA
Oxalo-acetate
Citrate
Isocitrate
Isocitrato Deshidrogenasa
⊖ ATP and NADH
⊕ ADP
Malate
Fumarate
Succinate
α-Ketoglutarate
Succinyl CoA


Pyruvate
⊖ ATP, acetyl CoA and NADH
Acetyl CoA
Oxalo-acetate
Citrate
Malate
Isocitrate
Fumarate
⊖ ATP and NADH
⊕ ADP
α-cetoglutarato Deshidrogenasa
Succinate
α-Ketoglutarate
Succinyl CoA
⊖ ATP, succinyl CoA, and NADH



Piruvato Deshidrogenasa
Pyruvate
⊖ ATP, acetyl CoA and NADH
Acetyl CoA
Oxalo-acetate
Citrate
Isocitrato Deshidrogenasa
Malate
Isocitrate
⊖ ATP and NADH
⊕ ADP
Fumarate
α-cetoglutarato Deshidrogenasa
Succinate
α-Ketoglutarate
Succinyl CoA
⊖ ATP, succinyl CoA, and NADH

Funciones biosintéticas del Ciclo de Krebs



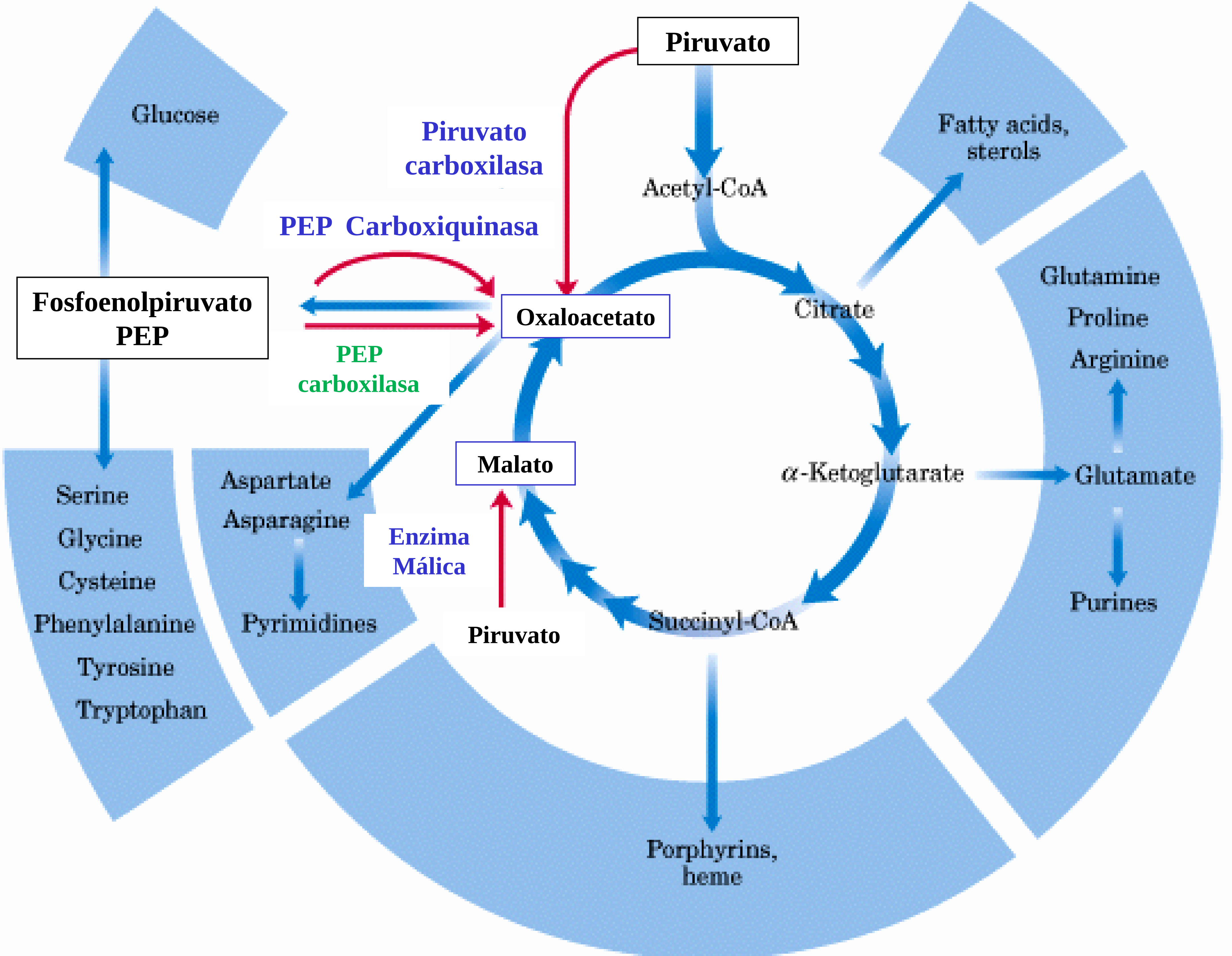
Piruvato
Acetil-CoA
Purinas
Pirimidinas
Otros aminoácidos
Oxaloacetato
Aspartato
Citrato
Ácidos grasos
Purinas
α-cetoglutarato
Succinil-CoA
Otros
aminoácidos
Porfirinas
Hemo
clorofila
Glutamato

El Ciclo de Krebs es

ANFIBÓLICO

Recuperación de intermediarios del Ciclo de Krebs

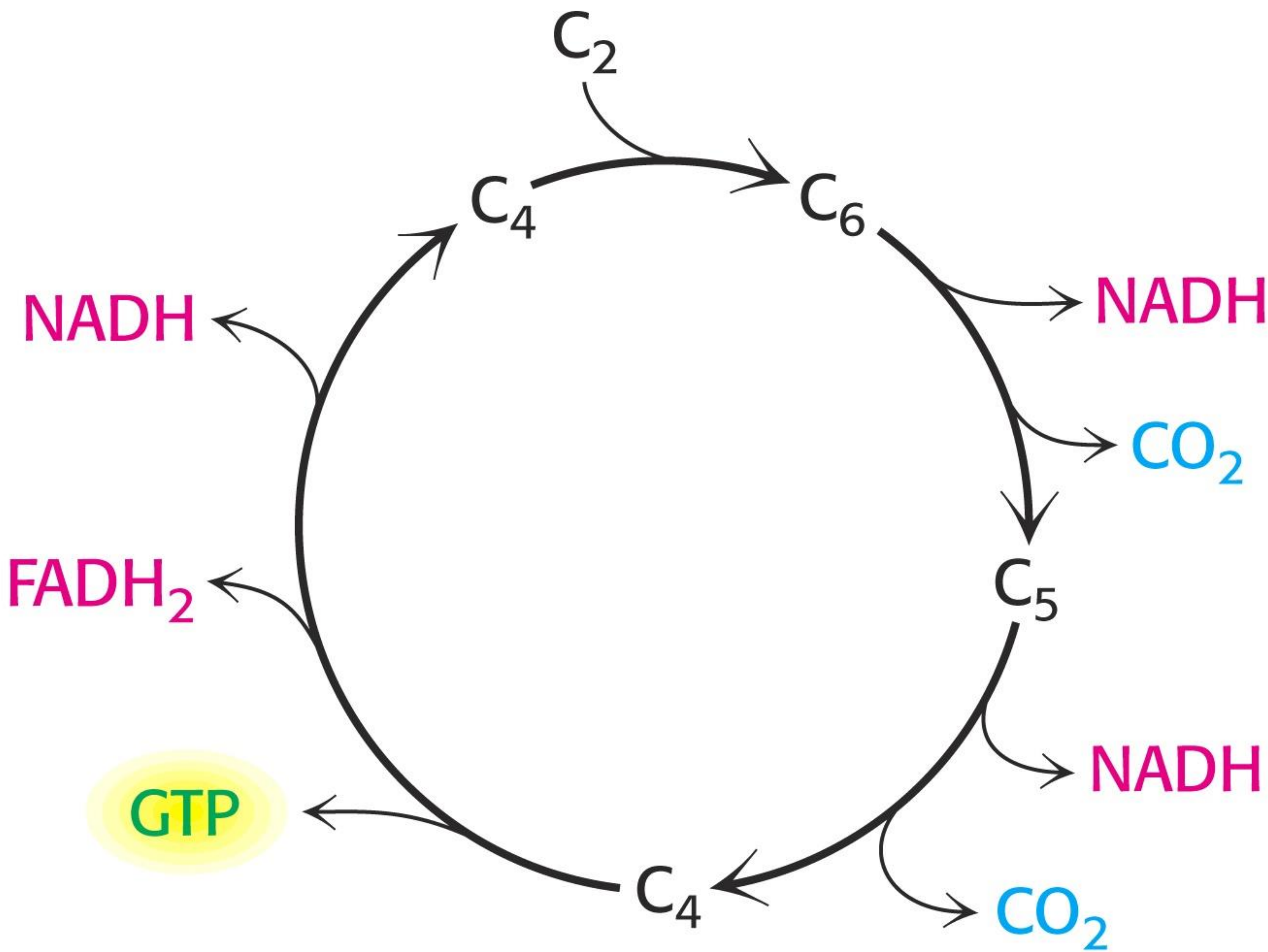
Reacciones Anapleróticas



Piruvato
Glucose
Piruvato carboxilasa
Acetyl-CoA
Fatty acids, sterols
PEP Carboxiquinasa
Fosfoenolpiruvato PEP
Oxaloacetato
Citrate
Glutamine
Proline
Arginine
PEP carboxilasa
Malato
α-Ketoglutarate
Glutamate
Serine
Glycine
Cysteine
Phenylalanine
Tyrosine
Tryptophan
Aspartate
Asparagine
Pyrimidines
Enzima Málica
Piruvato
Succinyl-CoA
Purines
Porphyrins, heme

Reacciones Anapleróticas

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


C2
C4
C6
NADH
CO2
C5
NADH
CO2
C4
GTP
FADH2
NADH