GLUCONEOGENESI

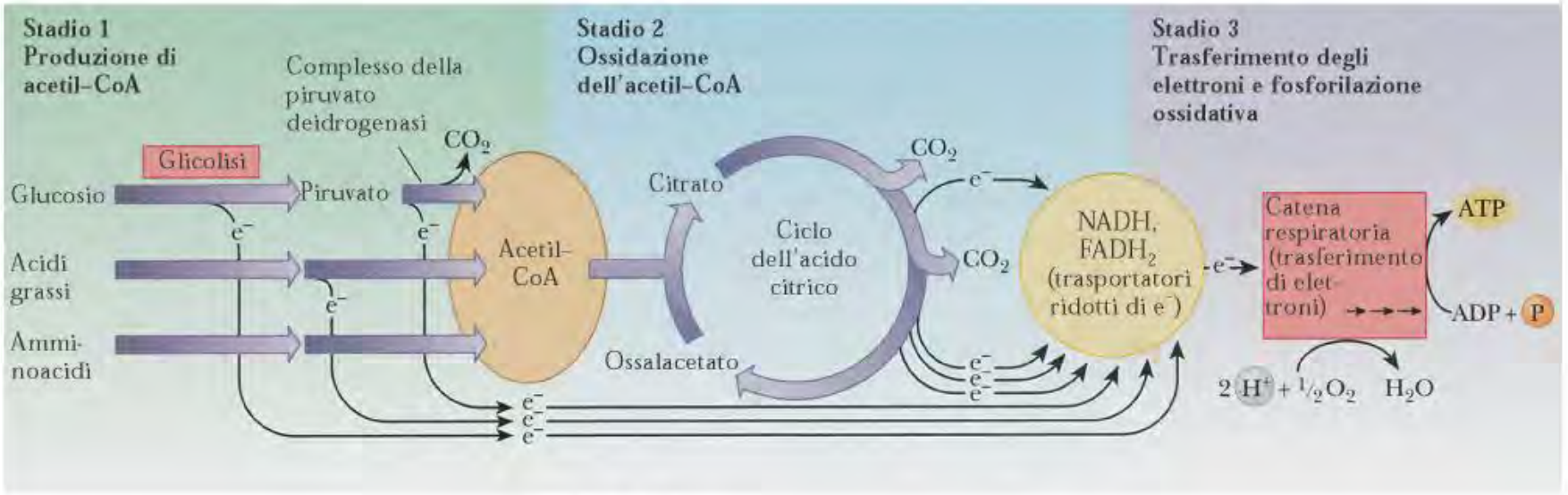
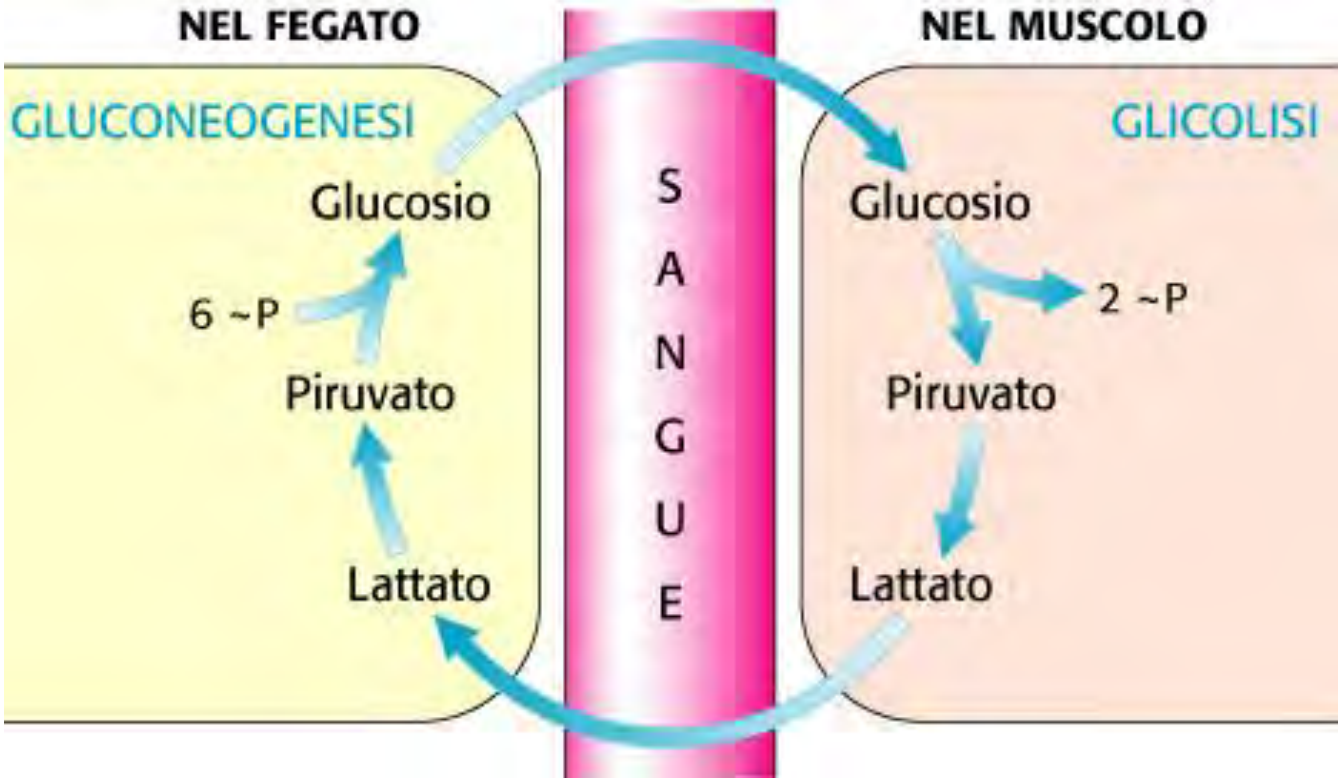


FIGURA 16.1
Il ciclo dell'acido citrico ha un ruolo centrale nel catabolismo. Gli amminoacidi, gli acidi grassi e il glucosio possono produrre tutti acetil-CoA nello stadio 1 del catabolismo. Nello stadio 2, l'acetil-CoA entra nel ciclo dell'acido citrico. Gli stadi 1 e 2 producono trasportatori di elettroni ridotti (qui mostrati come e^-). Nello stadio 3, gli elettroni entrano nella catena di trasporto degli elettroni, che produce ATP.

Campbell - Farrell
Biochimica
EdiSES


NEL FEGATO
GLUCONEOGENESI
Glucosio
6 ~P
Piruvato
Lattato
SANGUE
NEL MUSCOLO
GLICOLISI
Glucosio
2 ~P
Piruvato
Lattato

LA GLUCONEOGENESI

Sintesi de novo di molecole di glucosio

Avviene nel fegato a partire da
lattato,
piruvato
ossalacetato

che derivano dal catabolismo anaerobico del glucosio (in altri tessuti)
o da catabolismo degli aminoacidi

Rappresenta il principale meccanismo con cui il fegato produce e immette nel sangue glucosio durante il digiuno

Non è esattamente l'inverso della glicolisi,
anche se molte reazioni sono comuni

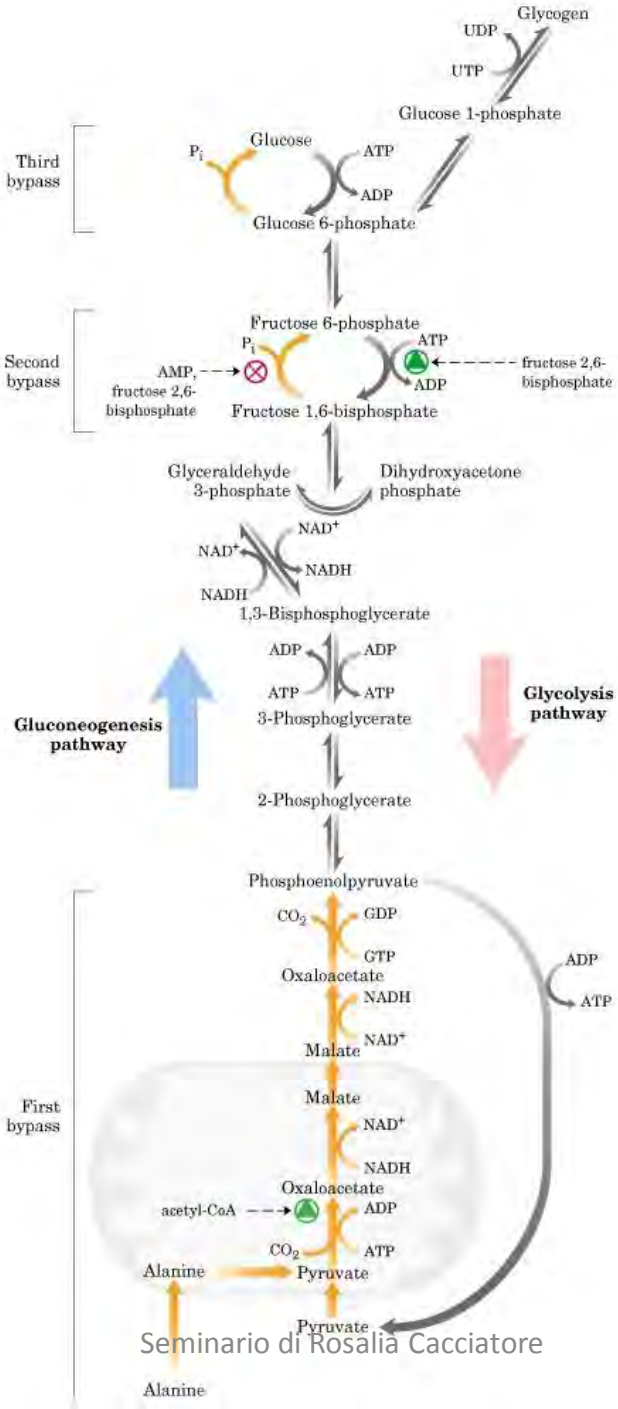
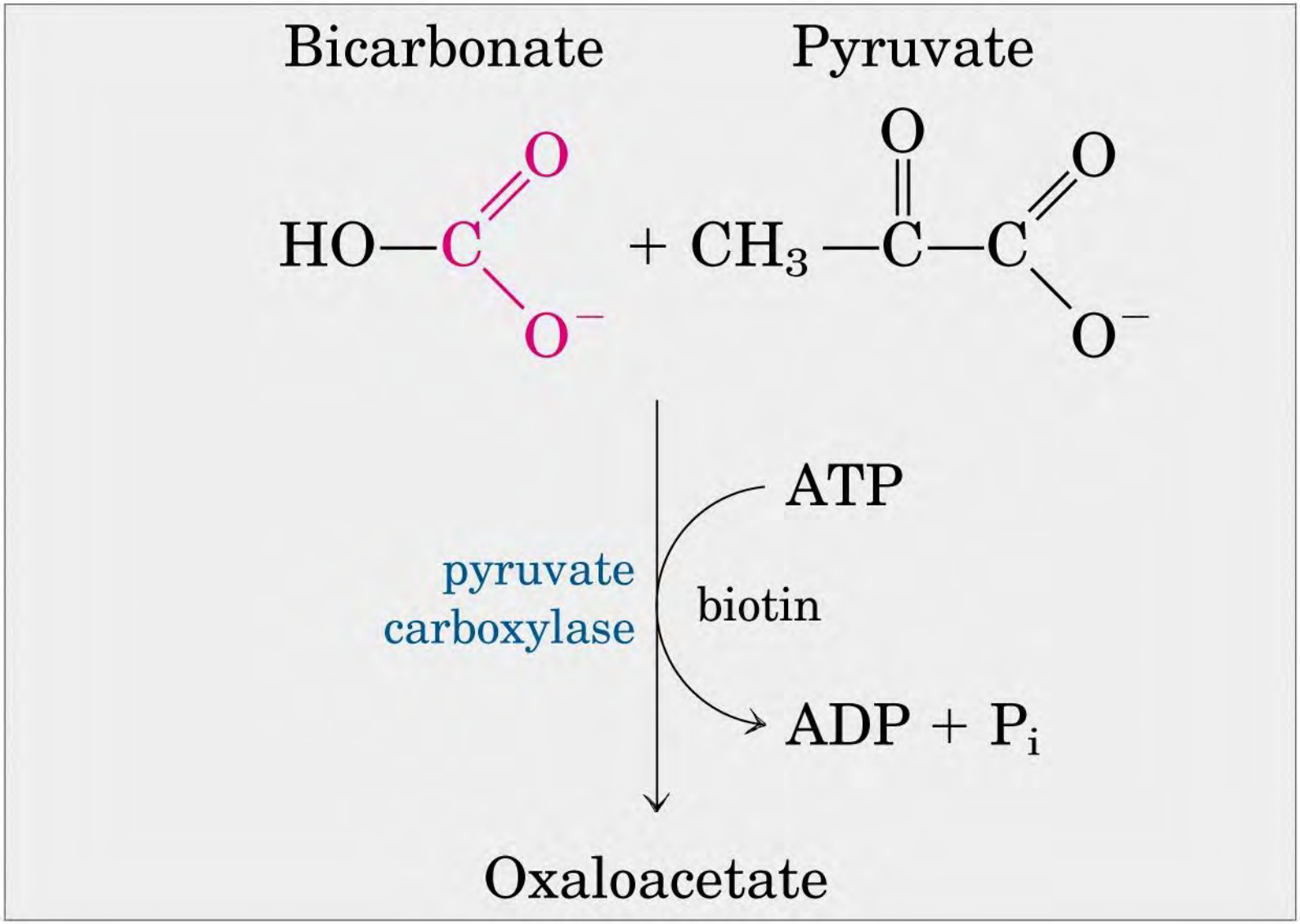

Glycogen
UDP
UTP
Glucose 1-phosphate
Third bypass
Glucose
ATP
ADP
Glucose 6-phosphate
Fructose 6-phosphate
Second bypass
AMP, fructose 2,6-bisphosphate
ATP
ADP
fructose 2,6-bisphosphate
Fructose 1,6-bisphosphate
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
NAD+
NADH
1,3-Bisphosphoglycerate
ADP
ATP
3-Phosphoglycerate
Gluconeogenesis pathway
Glycolysis pathway
2-Phosphoglycerate
Phosphoenolpyruvate
CO2
GDP
GTP
Oxaloacetate
NADH
NAD+
Malate
ADP
ATP
First bypass
Malate
NAD+
NADH
Oxaloacetate
acetyl-CoA
ADP
ATP
CO2
Alanine
Pyruvate
Pyruvate
Alanine

table 20–1

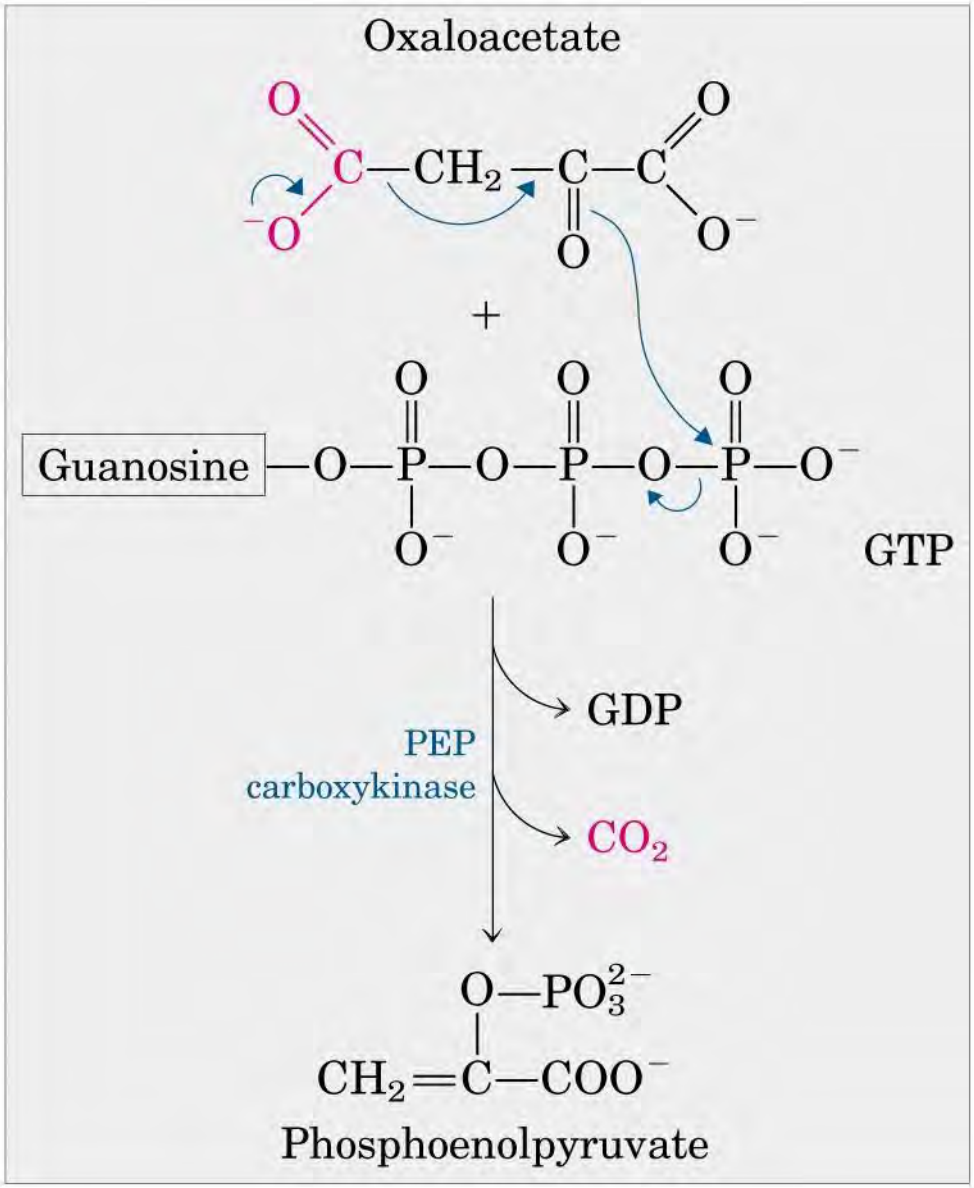
Free-Energy Changes of Glycolytic Reactions in Erythrocytes*

Glycolytic reaction step	$\Delta G'°$ (kJ/mol)	ΔG (kJ/mol)
① Glucose + ATP ⟶ glucose 6-phosphate + ADP + H^+	−16.7	−33.4
② Glucose 6-phosphate ⇌ fructose 6-phosphate	1.7	−2.5
③ Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP + H^+	−14.2	−22.2
④ Fructose 1,6-bisphosphate ⇌ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate	23.8	−1.25
⑤ Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate	7.5	2.5
⑥ Glyceraldehyde 3-phosphate + P_i + NAD^+ ⇌ 1,3-bisphosphoglycerate + NADH + H^+	6.3	−1.7
⑦ 1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP	−18.8	1.25
⑧ 3-Phosphoglycerate ⇌ 2-phosphoglycerate	4.4	0.8
⑨ 2-Phosphoglycerate ⇌ phosphoenolpyruvate + H_2O	7.5	−3.3
⑩ Phosphoenolpyruvate + ADP + H^+ ⟶ pyruvate + ATP	−31.4	−16.7

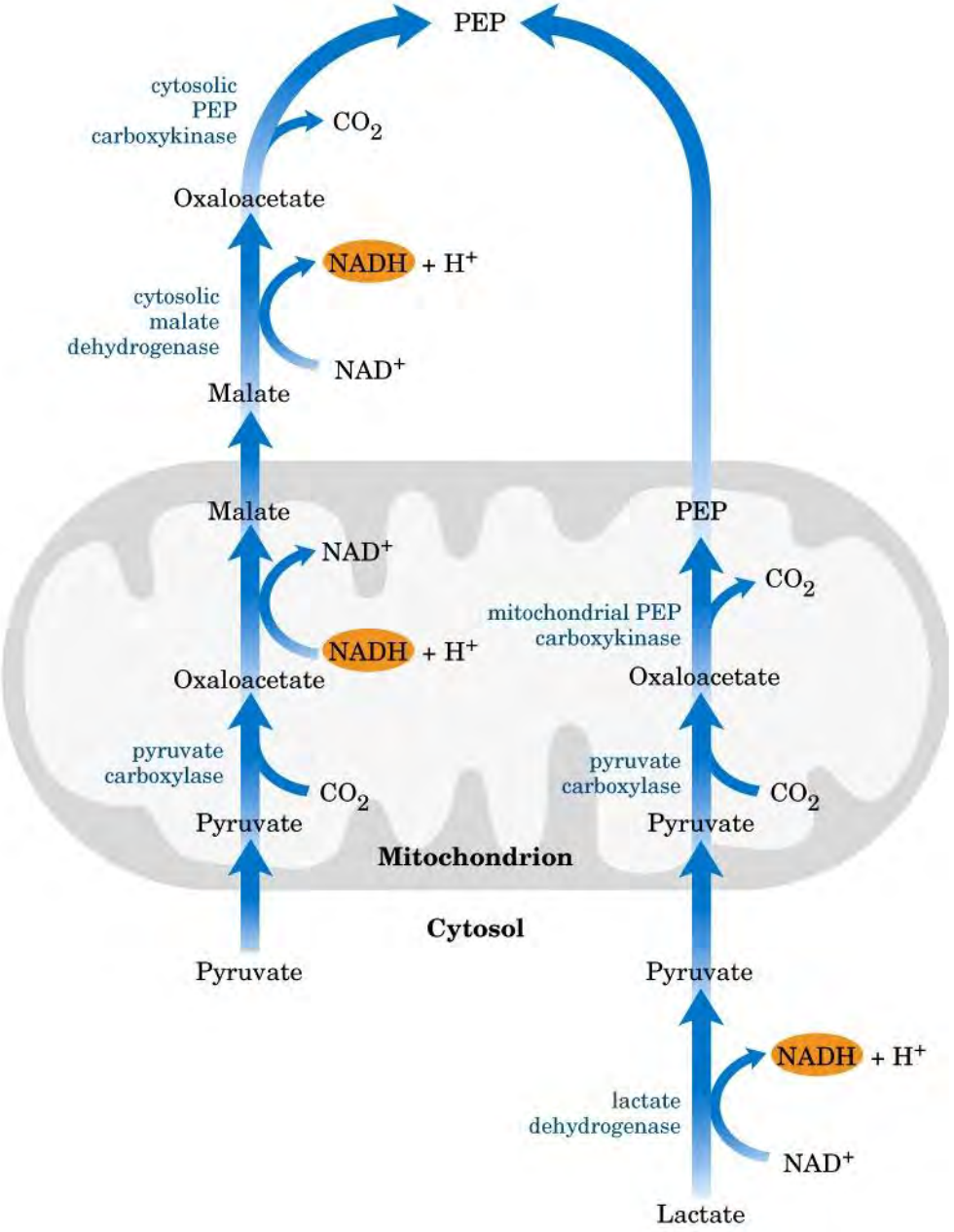
*$\Delta G'°$ is the standard free-energy change, as defined in Chapter 14 (see p. 494). At pH 7.0, ΔG is the free-energy change calculated from the actual concentrations of glycolytic intermediates present under physiological conditions in erythrocytes. The glycolytic reactions bypassed in gluconeogenesis are shown in red.

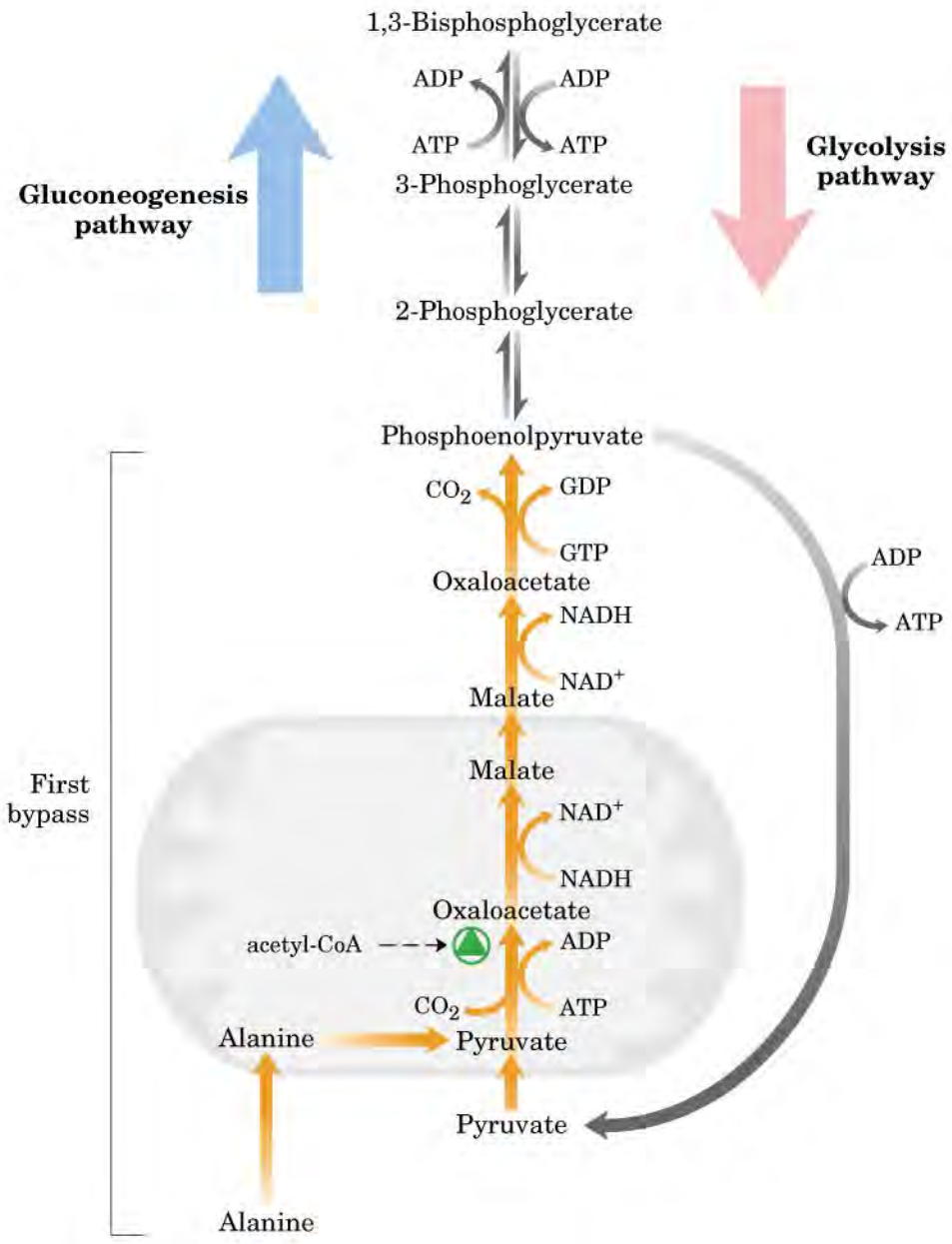

Bicarbonate
Pyruvate
HO—C
O
O⁻
+ CH3—C—C
O
O
O⁻
ATP
pyruvate carboxylase
biotin
ADP + Pi
Oxaloacetate

(a)


Oxaloacetate
Guanosine
GTP
GDP
PEP
carboxykinase
CO_2
Phosphoenolpyruvate

(b)


PEP
cytosolic
PEP
carboxykinase
CO_2
Oxaloacetate
NADH + H^+
cytosolic
malate
dehydrogenase
NAD^+
Malate
Malate
NAD^+
NADH + H^+
Oxaloacetate
pyruvate
carboxylase
CO_2
Pyruvate
PEP
CO_2
mitochondrial PEP
carboxykinase
Oxaloacetate
pyruvate
carboxylase
CO_2
Pyruvate
Mitochondrion
Cytosol
Pyruvate
Pyruvate
NADH + H^+
lactate
dehydrogenase
NAD^+
Lactate


1,3-Bisphosphoglycerate
ADP
ADP
ATP
ATP
3-Phosphoglycerate
Gluconeogenesis pathway
Glycolysis pathway
2-Phosphoglycerate
Phosphoenolpyruvate
CO_2
GDP
GTP
Oxaloacetate
ADP
ATP
NADH
NAD^+
Malate
First bypass
Malate
NAD^+
NADH
Oxaloacetate
acetyl-CoA
ADP
CO_2
ATP
Alanine
Pyruvate
Pyruvate
Alanine

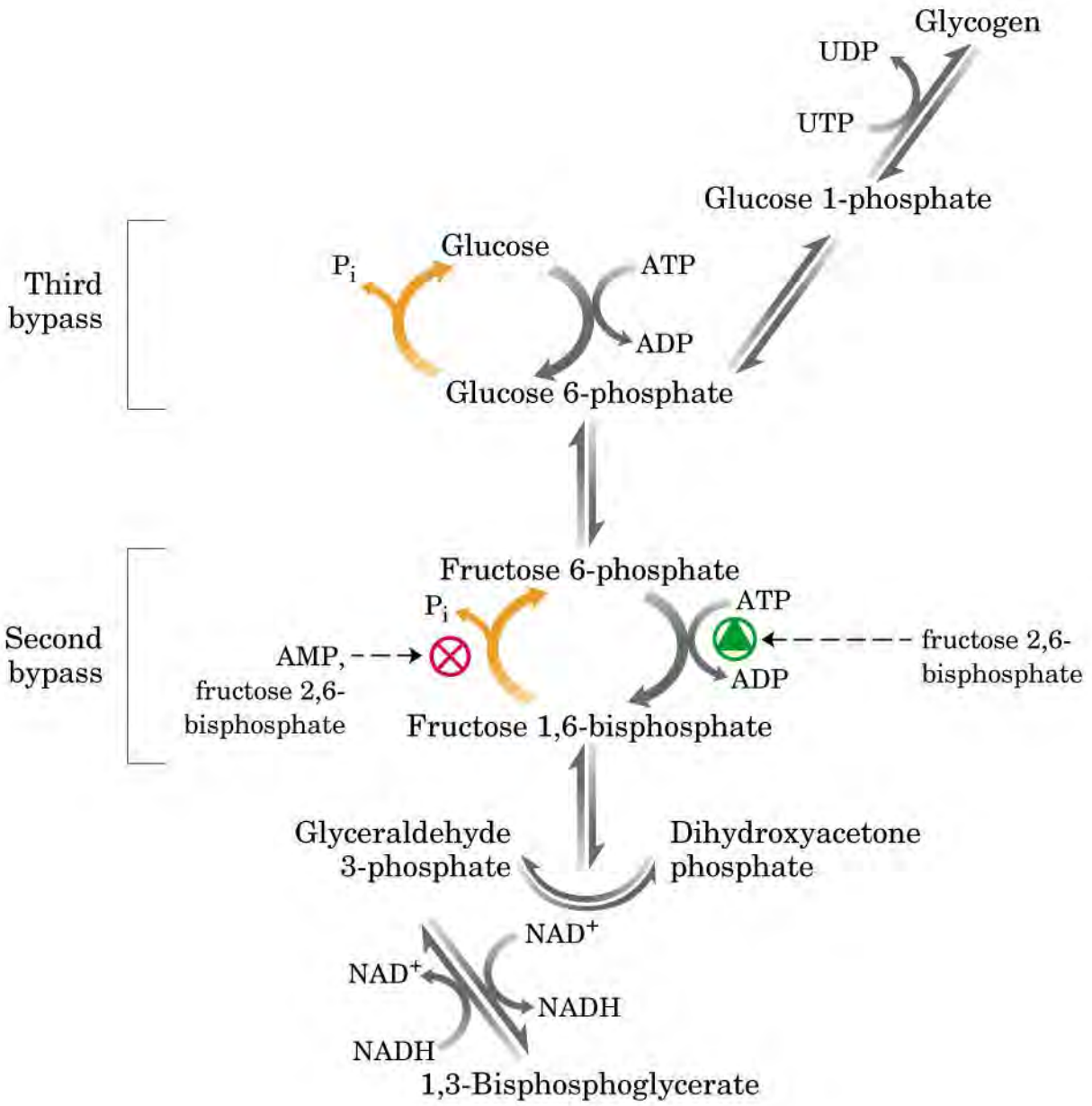

Glycogen
UDP
UTP
Glucose 1-phosphate
Third bypass
P_i
Glucose
ATP
ADP
Glucose 6-phosphate
Fructose 6-phosphate
Second bypass
P_i
ATP
AMP, fructose 2,6-bisphosphate
fructose 2,6-bisphosphate
ADP
Fructose 1,6-bisphosphate
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
NAD^+
NAD^+
NADH
NADH
1,3-Bisphosphoglycerate

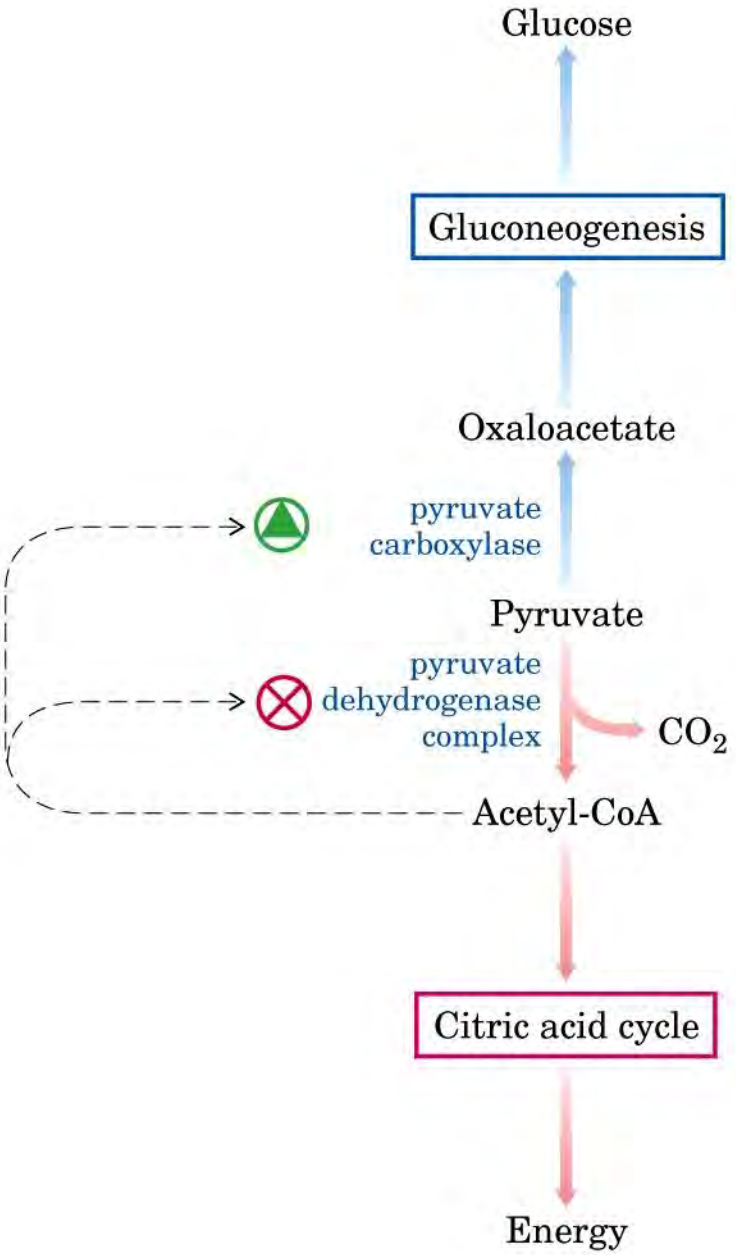
table 20–2

Sequential Reactions in Gluconeogenesis Starting from Pyruvate*

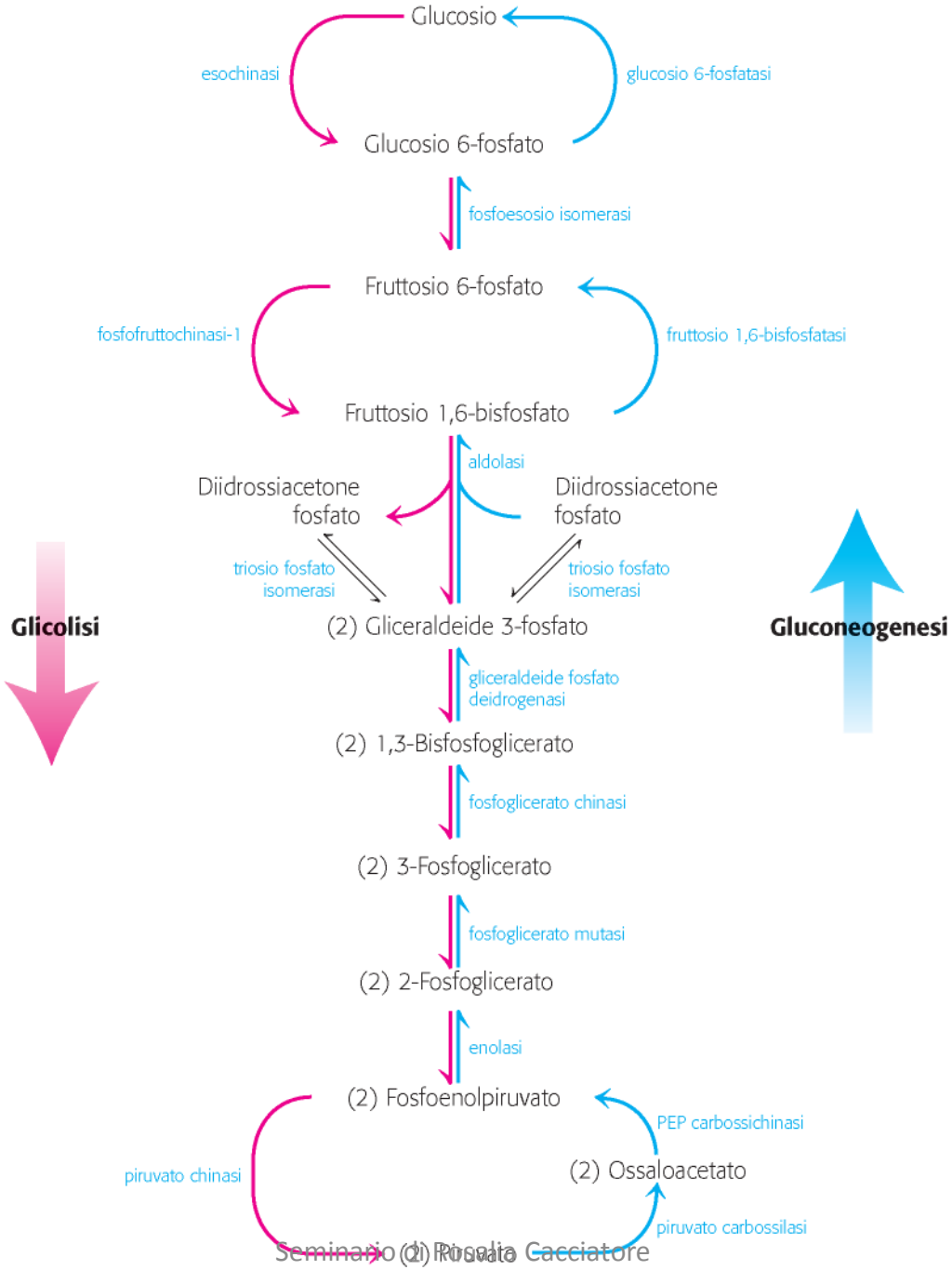
Pyruvate + HCO_3^- + ATP ⟶ oxaloacetate + ADP + P_i + H^+	×2
Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO_2 + GDP	×2
Phosphoenolpyruvate + H_2O ⇌ 2-phosphoglycerate	×2
2-Phosphoglycerate ⇌ 3-phosphoglycerate	×2
3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP + H^+	×2
1,3-Bisphosphoglycerate + NADH + H^+ ⇌ glyceraldehyde 3-phosphate + NAD^+ + P_i	×2
Glyceraldehyde 3-phosphate ⇌ dihydroxyacetone phosphate	
Glyceraldehyde 3-phosphate + dihydroxyacetone phosphate ⇌ fructose 1,6-bisphosphate	
Fructose 1,6-bisphosphate + H_2O ⟶ fructose 6-phosphate + P_i	
Fructose 6-phosphate ⇌ glucose 6-phosphate	
Glucose 6-phosphate + H_2O ⟶ glucose + P_i	

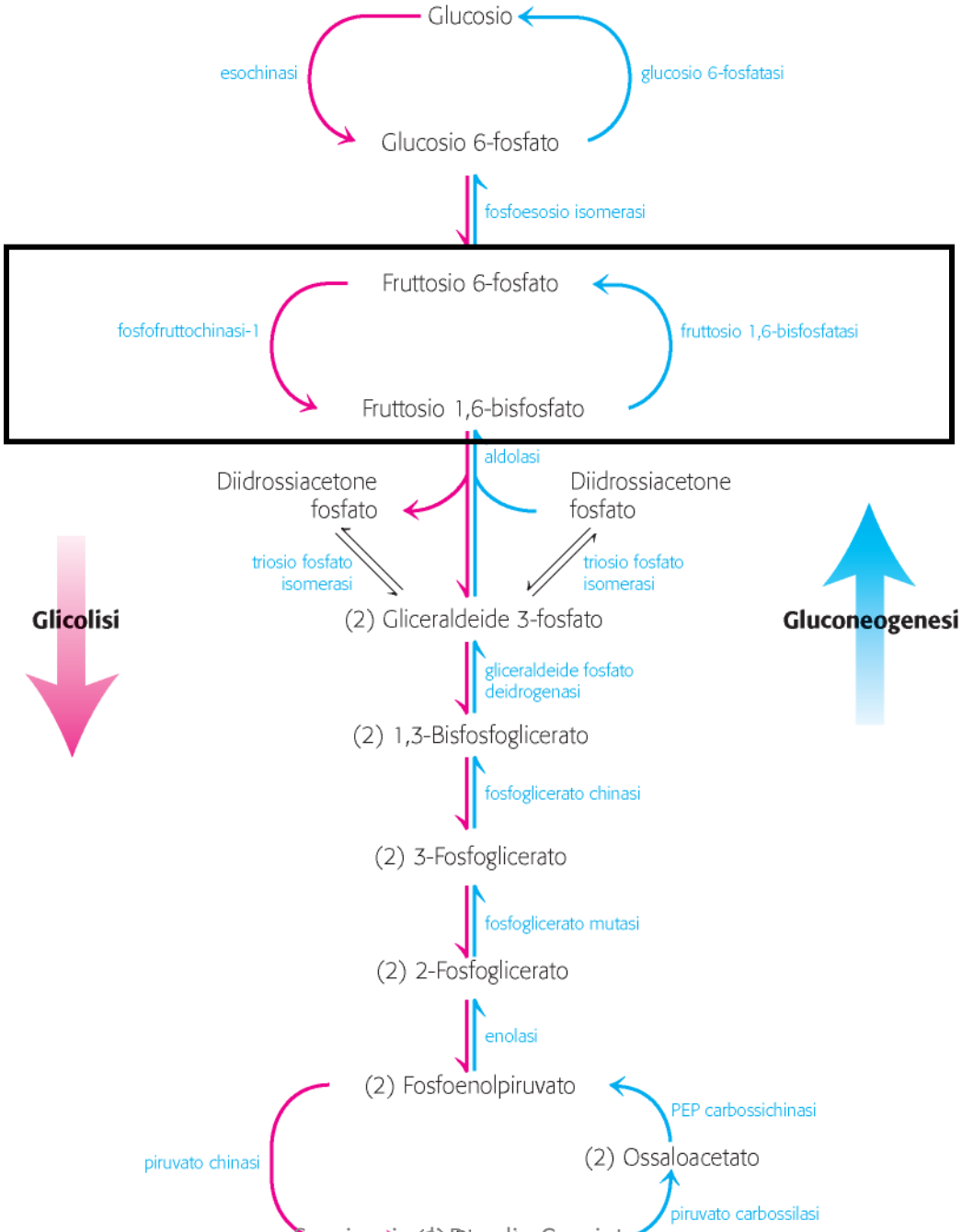
Sum: 2 Pyruvate + 4ATP + 2GTP + 2NADH + $4H_2O$ ⟶ glucose + 4ADP + 2GDP + $6P_i$ + $2NAD^+$ + $2H^+$

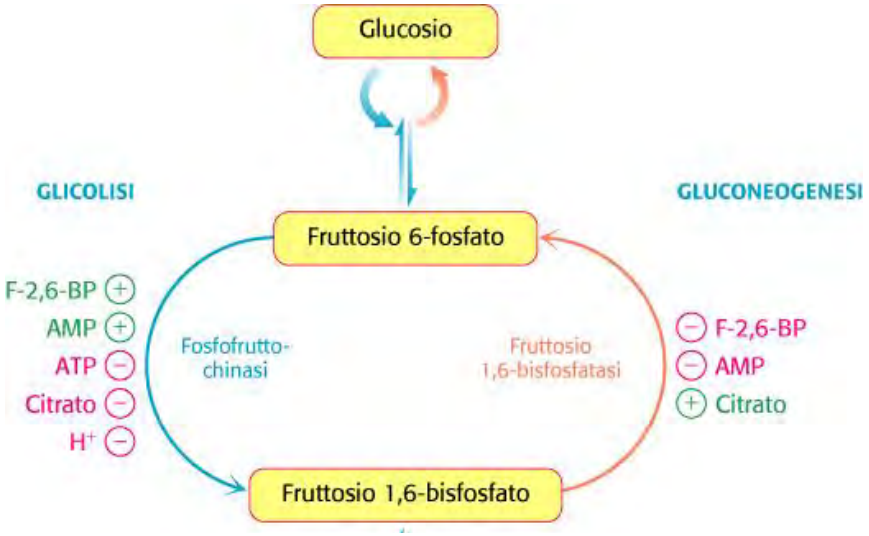
*The bypass reactions are in red; all other reactions are reversible steps of glycolysis. The figures at the right indicate that the reaction is to be counted twice, because two three-carbon precursors are required to make a molecule of glucose. Note that the reactions required to replace the cytosolic NADH consumed in the glyceraldehyde 3-phosphate dehydrogenase reaction (the conversion of lactate to pyruvate in the cytosol or the transport of reducing equivalents from mitochondria to the cytosol in the form of malate) are not considered in this summary.


Glucose
Gluconeogenesis
Oxaloacetate
pyruvate carboxylase
Pyruvate
pyruvate dehydrogenase complex
CO_2
Acetyl-CoA
Citric acid cycle
Energy

REGOLAZIONE DELLA GLICOLISI E DELLA GLUCONEOGENESI NEL FEGATO DA PARTE DEL GLUCAGONE

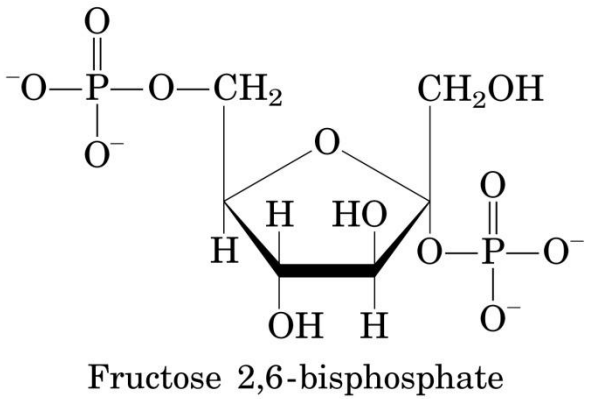

Glucosio
esochinasi
glucosio 6-fosfatasi
Glucosio 6-fosfato
fosfoesosio isomerasi
Fruttosio 6-fosfato
fosfofruttochinasi-1
fruttosio 1,6-bisfosfatasi
Fruttosio 1,6-bisfosfato
aldolasi
Diidrossiacetone fosfato
Diidrossiacetone fosfato
triosio fosfato isomerasi
triosio fosfato isomerasi
Glicolisi
(2) Gliceraldeide 3-fosfato
Gluconeogenesi
gliceraldeide fosfato deidrogenasi
(2) 1,3-Bisfosfoglicerato
fosfoglicerato chinasi
(2) 3-Fosfoglicerato
fosfoglicerato mutasi
(2) 2-Fosfoglicerato
enolasi
(2) Fosfoenolpiruvato
PEP carbossichinasi
piruvato chinasi
(2) Ossaloacetato
piruvato carbossilasi
(2) Piruvato


Glucosio
esochinasi
glucosio 6-fosfatasi
Glucosio 6-fosfato
fosfoesosio isomerasi
Fruttosio 6-fosfato
fosfofruttochinasi-1
fruttosio 1,6-bisfosfatasi
Fruttosio 1,6-bisfosfato
aldolasi
Diidrossiacetone fosfato
Diidrossiacetone fosfato
triosio fosfato isomerasi
triosio fosfato isomerasi
Glicolisi
(2) Gliceraldeide 3-fosfato
Gluconeogenesi
gliceraldeide fosfato deidrogenasi
(2) 1,3-Bisfosfoglicerato
fosfoglicerato chinasi
(2) 3-Fosfoglicerato
fosfoglicerato mutasi
(2) 2-Fosfoglicerato
enolasi
(2) Fosfoenolpiruvato
PEP carbossichinasi
piruvato chinasi
(2) Ossaloacetato
piruvato carbossilasi
(2) Piruvato

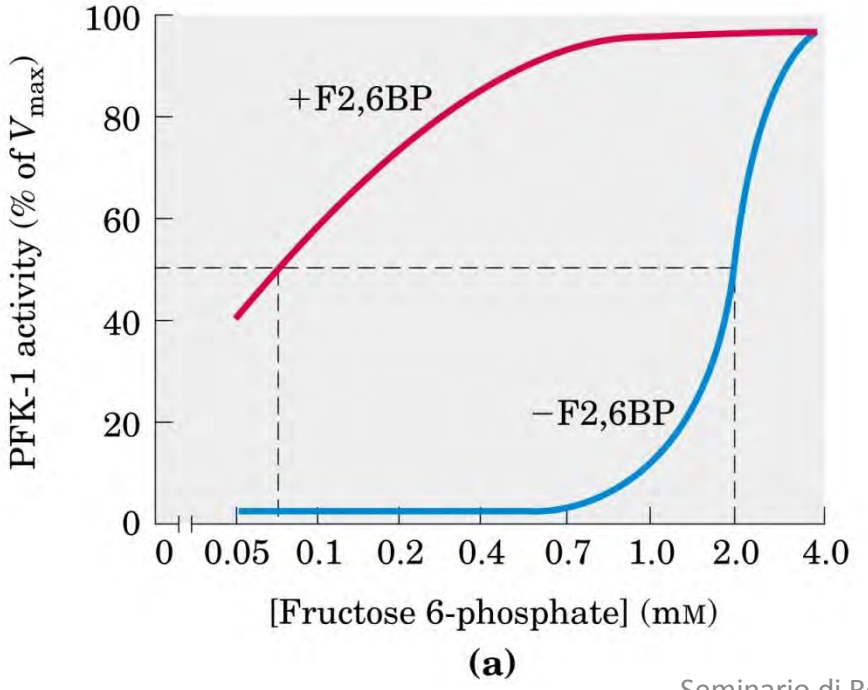

Glucosio
GLICOLISI
GLUCONEOGENESI
Fruttosio 6-fosfato
F-2,6-BP ⊕
AMP ⊕
ATP ⊖
Citrato ⊖
H+ ⊖
Fosfofrutto-chinasi
Fruttosio 1,6-bisfosfatasi
⊖ F-2,6-BP
⊖ AMP
⊕ Citrato
Fruttosio 1,6-bisfosfato

IL FRUTTOSIO 2,6 BISFOSFATO E' UN

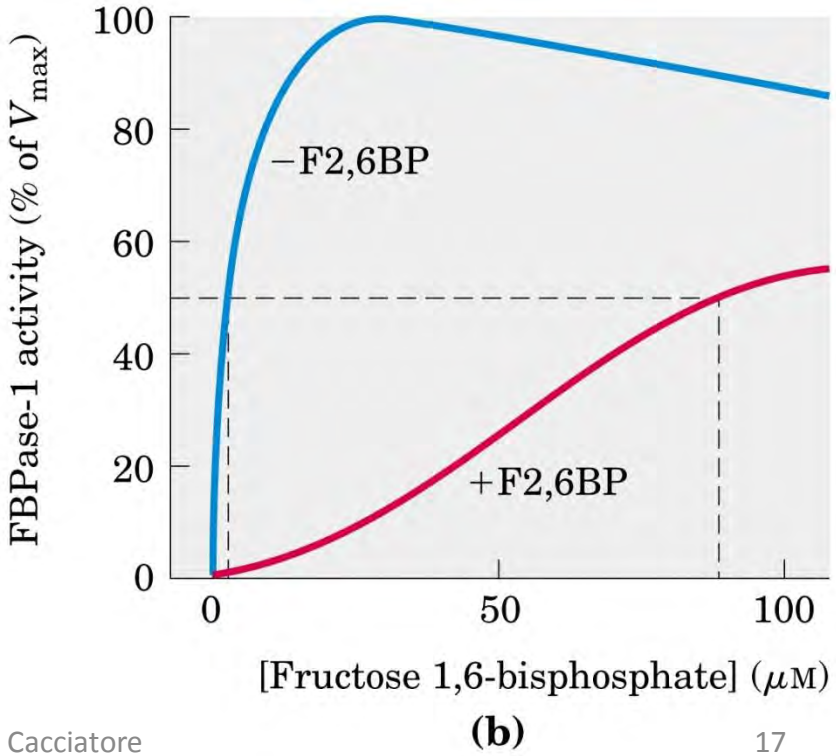
ATTIVATORE ALLOSTERICO DELLA PFK-1
(quindi stimola la glicolisi)
E UN
INIBITORE ALLOSTERICO DELLA FBPasi-1
(quindi inibisce la gluconeogenesi)



Fructose 2,6-bisphosphate



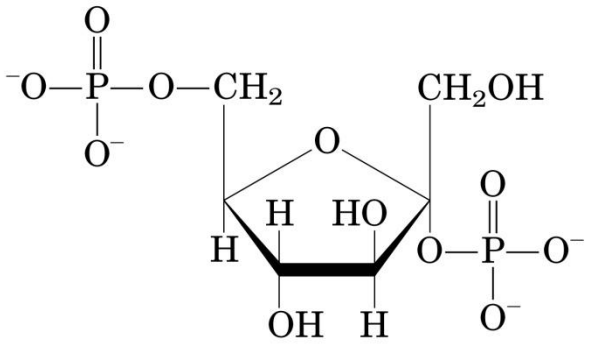
(a)



(b)

IL <u>FRUTTOSIO 2,6 BISFOSFATO</u> E' UN

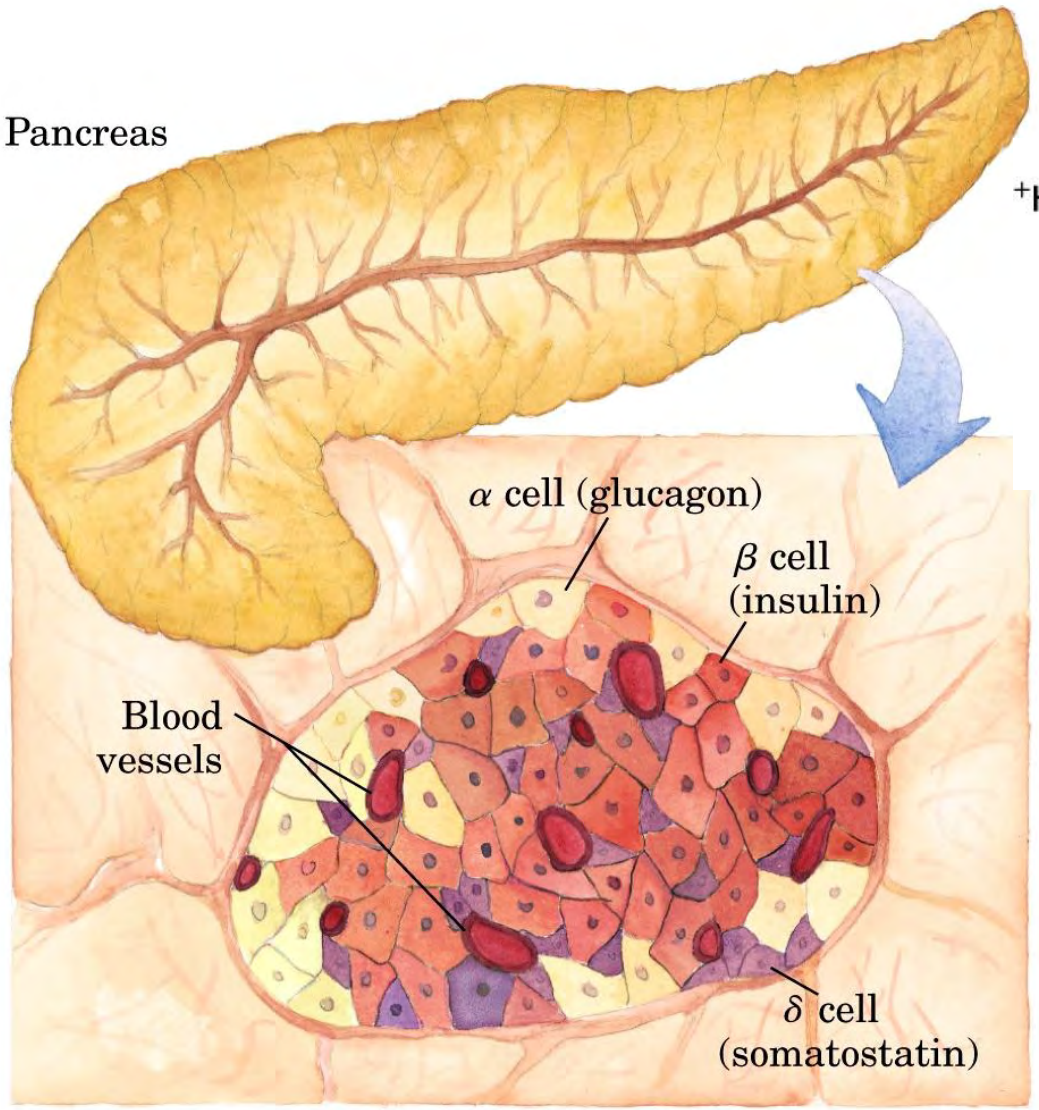
ATTIVATORE ALLOSTERICO DELLA PFK-1
(quindi <u>stimola la glicolisi</u>)
E UN
INIBITORE ALLOSTERICO DELLA FBPasi-1
(quindi <u>inibisce la gluconeogenesi</u>)



Fructose 2,6-bisphosphate

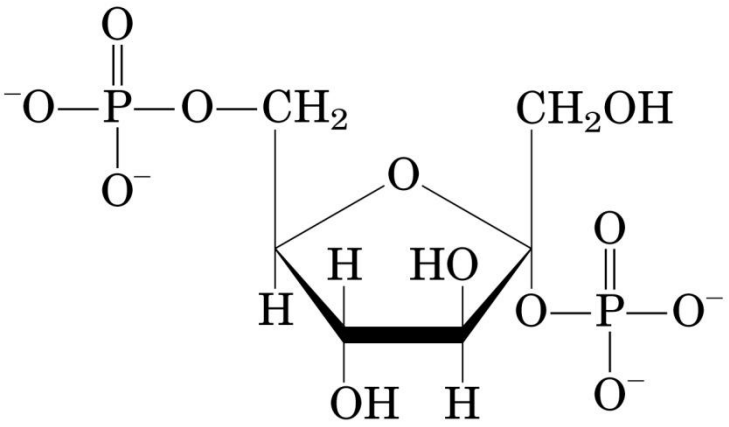
I LIVELLI DI FRUTTOSIO 2,6 BISFOSFATO
SONO REGOLATI DAL GLUCAGONE

IL GLUCAGONE
<u>RIDUCE</u> I LIVELLI DI FRUTTOSIO 2,6 BISFOSFATO
E QUINDI
<u>STIMOLA</u> LA GLUCONEOGENESI ED
<u>INIBISCE</u> LA GLICOLISI NEL FEGATO

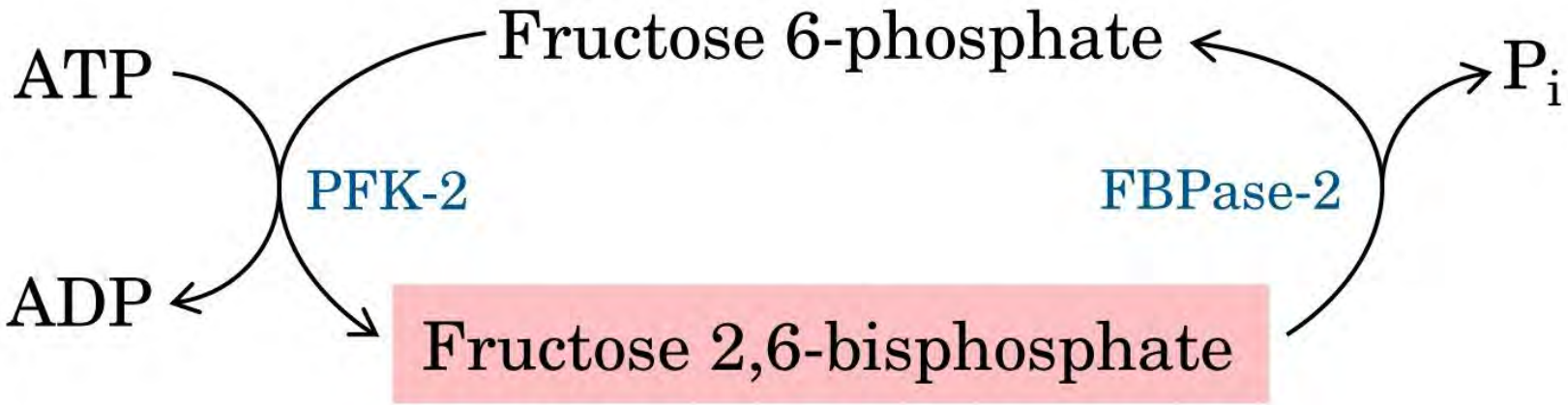


5 10
$^{+}H_3N$–His–Ser–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Tyr–
15 20
–Ser–Lys–Tyr–Leu–Asp–Ser–Arg–Arg–Ala–Gln–
25 29
–Asp–Phe–Val–Gln–Trp–Leu–Met–Asn–Thr–COO^{-}

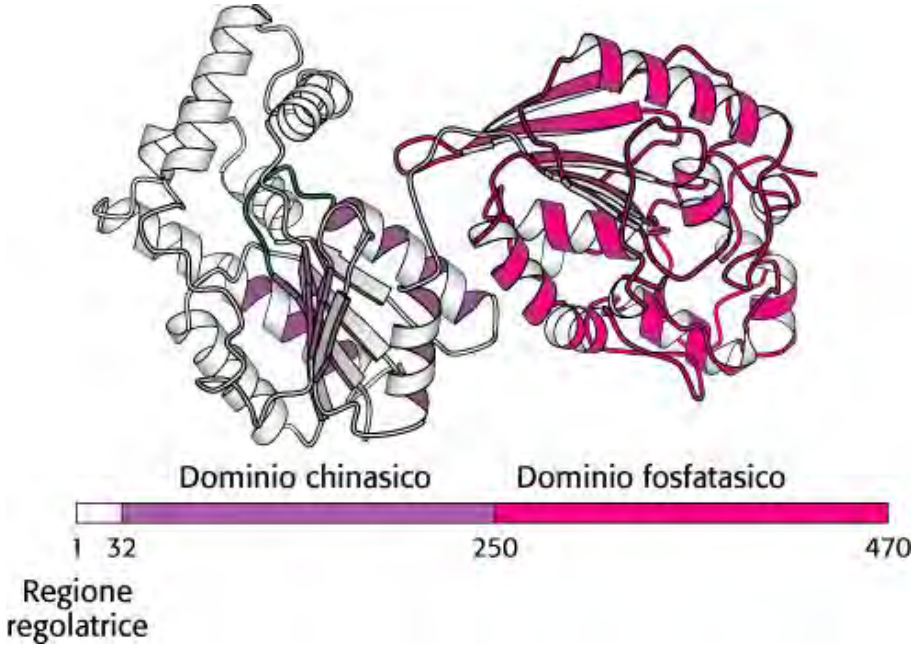
Glucagone

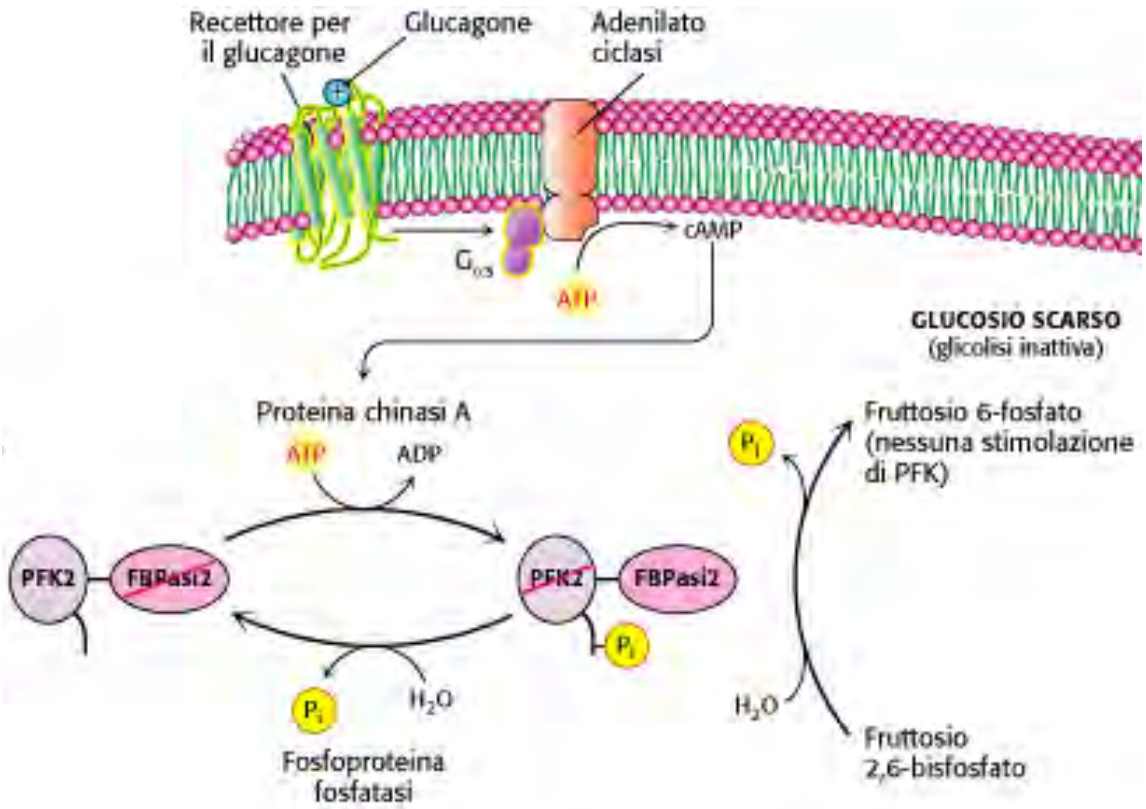


Fructose 2,6-bisphosphate

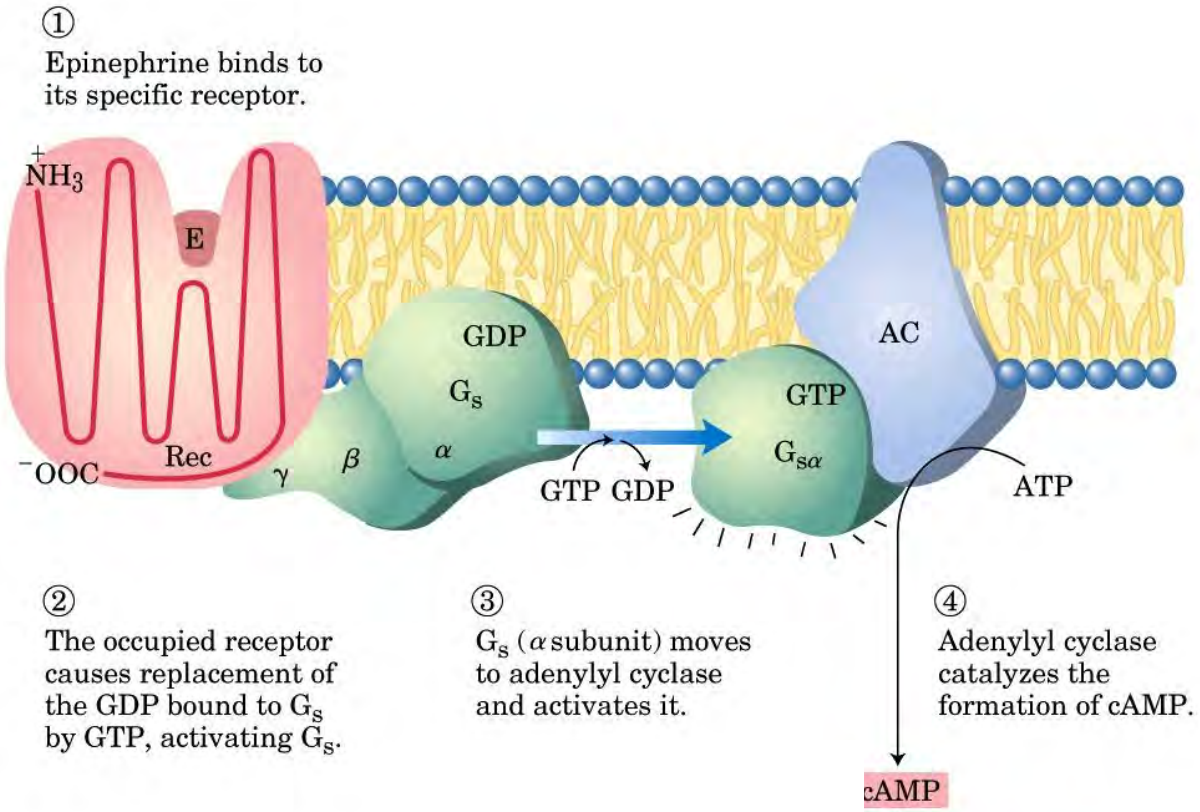


(a)


Dominio chinasico
Dominio fosfatasico
1
32
250
470
Regione
regolatrice


Recettore per il glucagone
Glucagone
Adenilato ciclasi
cAMP
ATP
GLUCOSIO SCARSO
(glicolisi inattiva)
Proteina chinasi A
ATP
ADP
PFK2
FBPasi2
PFK2
FBPasi2
P_i
H_2O
P_i
Fosfoproteina fosfatasi
P_i
Fruttosio 6-fosfato (nessuna stimolazione di PFK)
H_2O
Fruttosio 2,6-bisfosfato

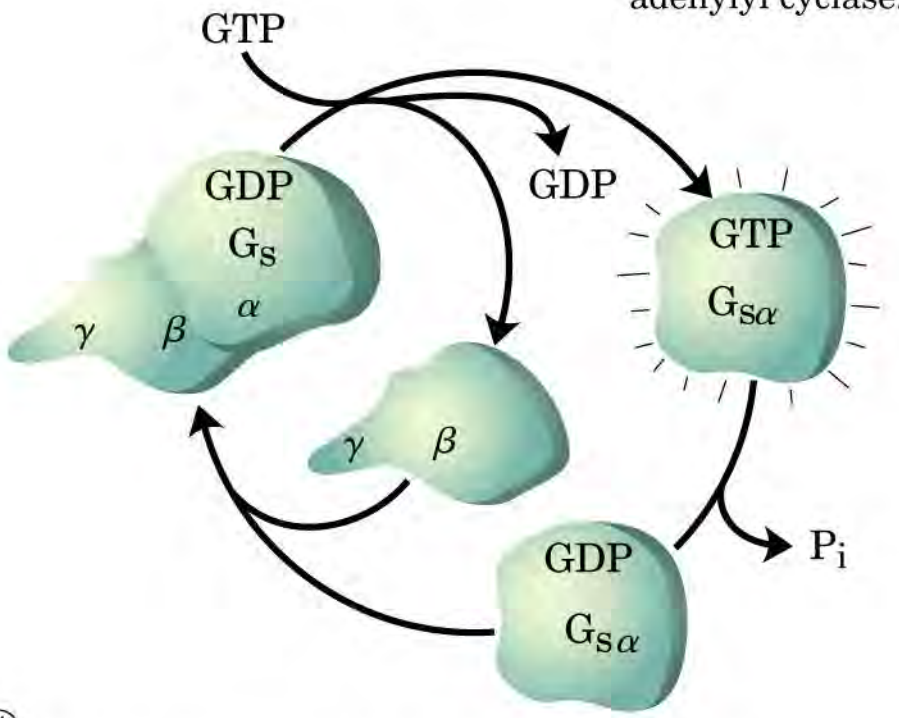
RECETTORE PER L'ADRENALINA, PROTEINE G, ED ADENILATO CICLASI



① G_S with GDP bound is turned off; it cannot activate adenylyl cyclase.

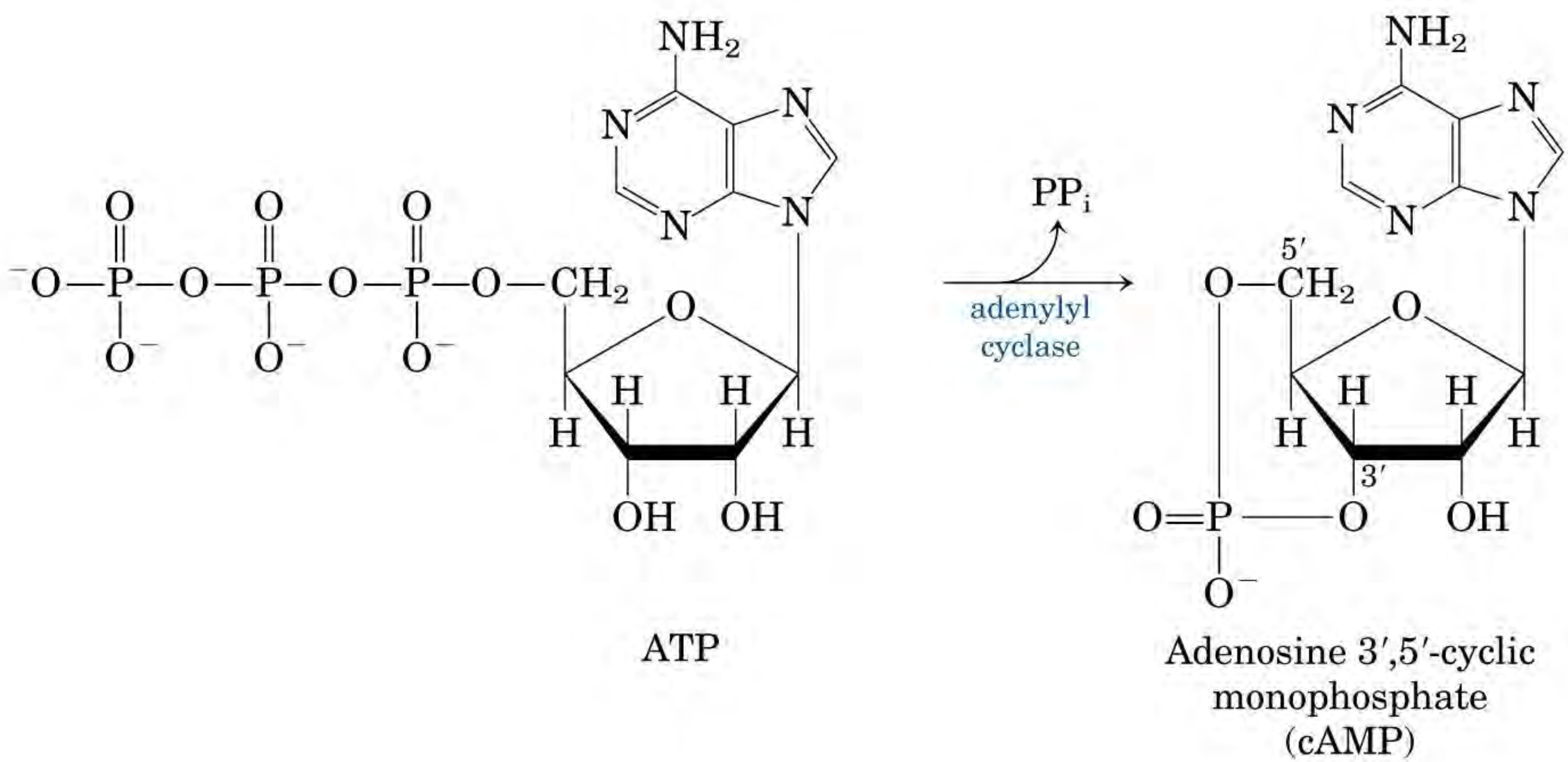
② Contact of G_S with hormone-receptor complex causes displacement of bound GDP by GTP.

③ G_S with GTP bound dissociates into α and βγ subunits. $G_{S\alpha}$-GTP is turned on; it can activate adenylyl cyclase.

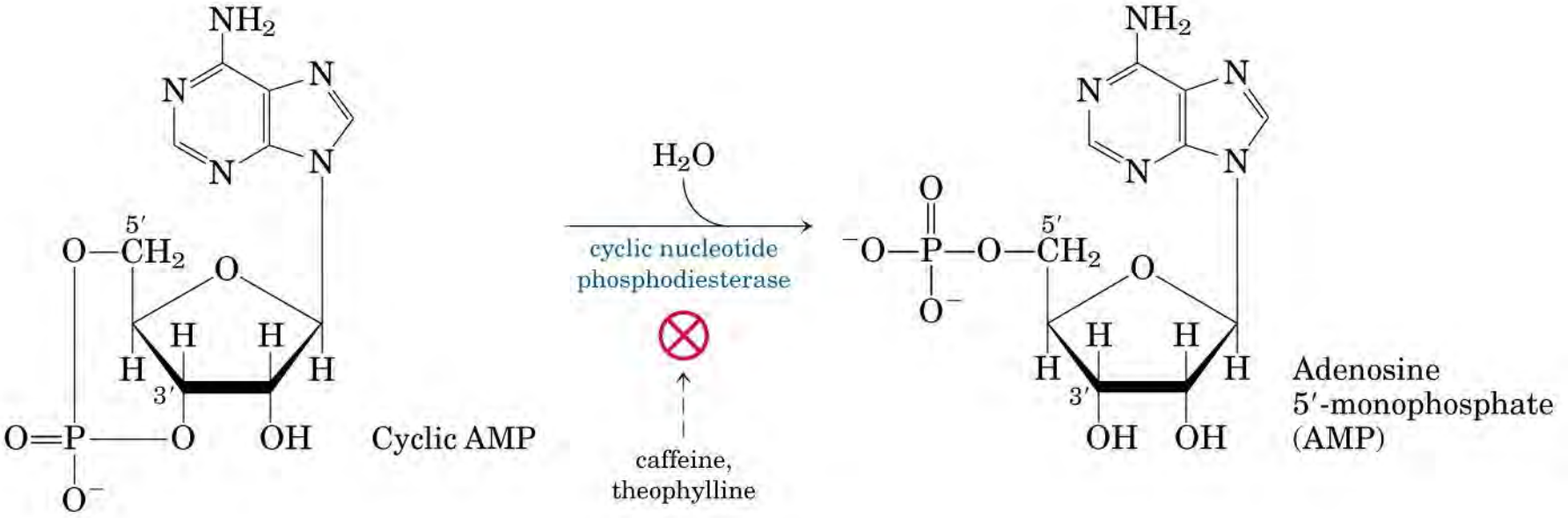


④ GTP bound to $G_{S\alpha}$ is hydrolyzed by the protein's intrinsic GTPase; $G_{S\alpha}$ thereby turns itself off. The inactive α subunit reassociates with the β, γ subunits.

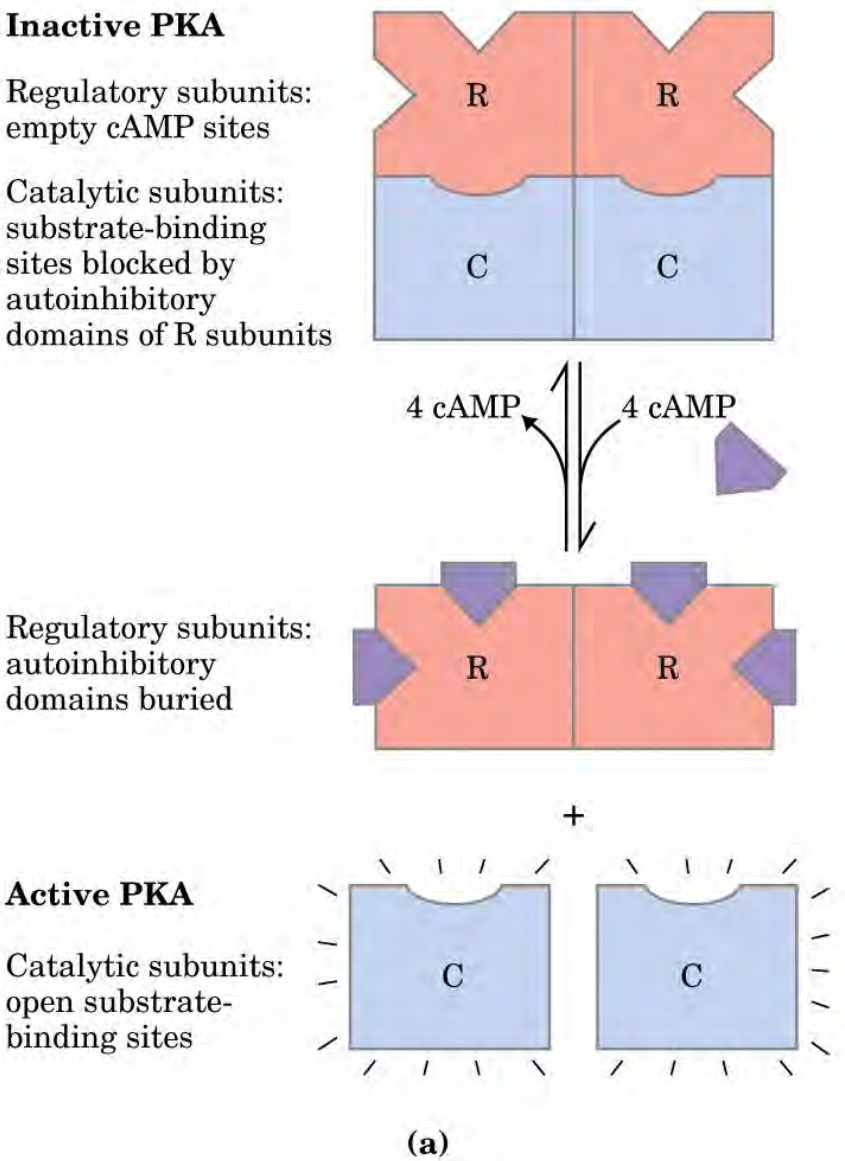
AMP CICLICO (cAMP)
sintesi



AMP CICLICO (cAMP)
degradazione

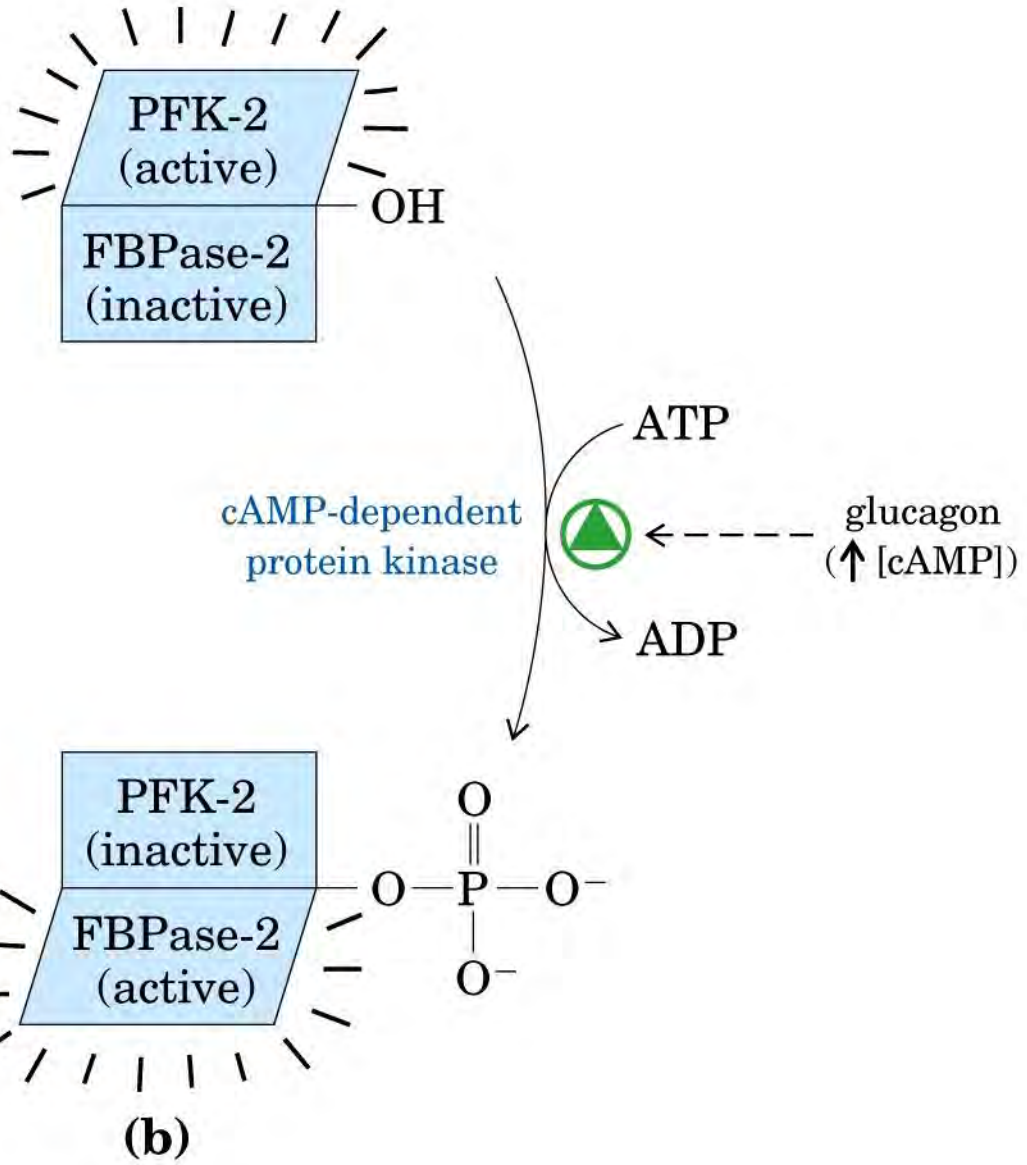


Il cAMP attiva la protein chinasi cAMP-dipendente (PKA)



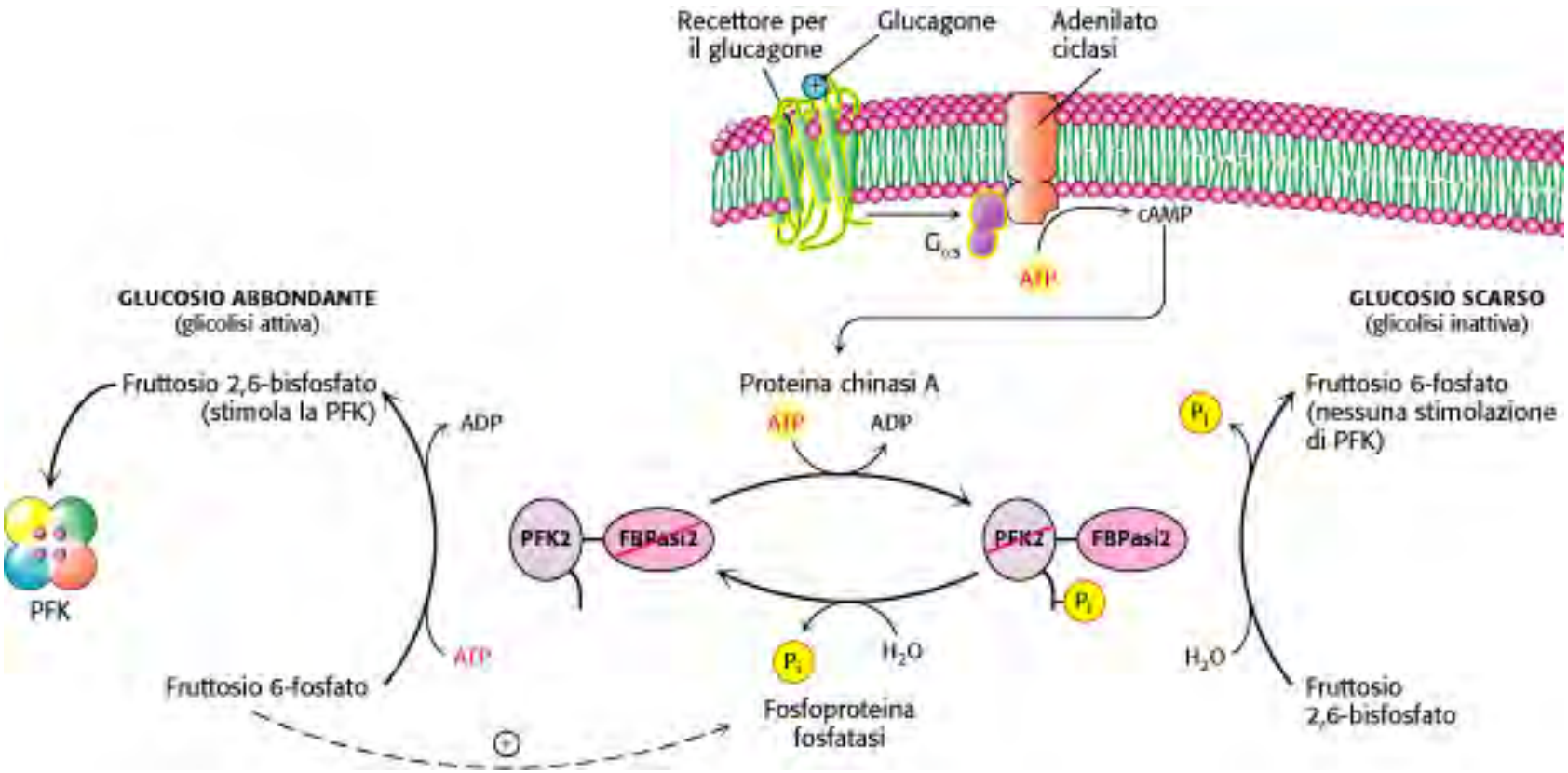
↑[Fructose 2,6-bisphosphate]

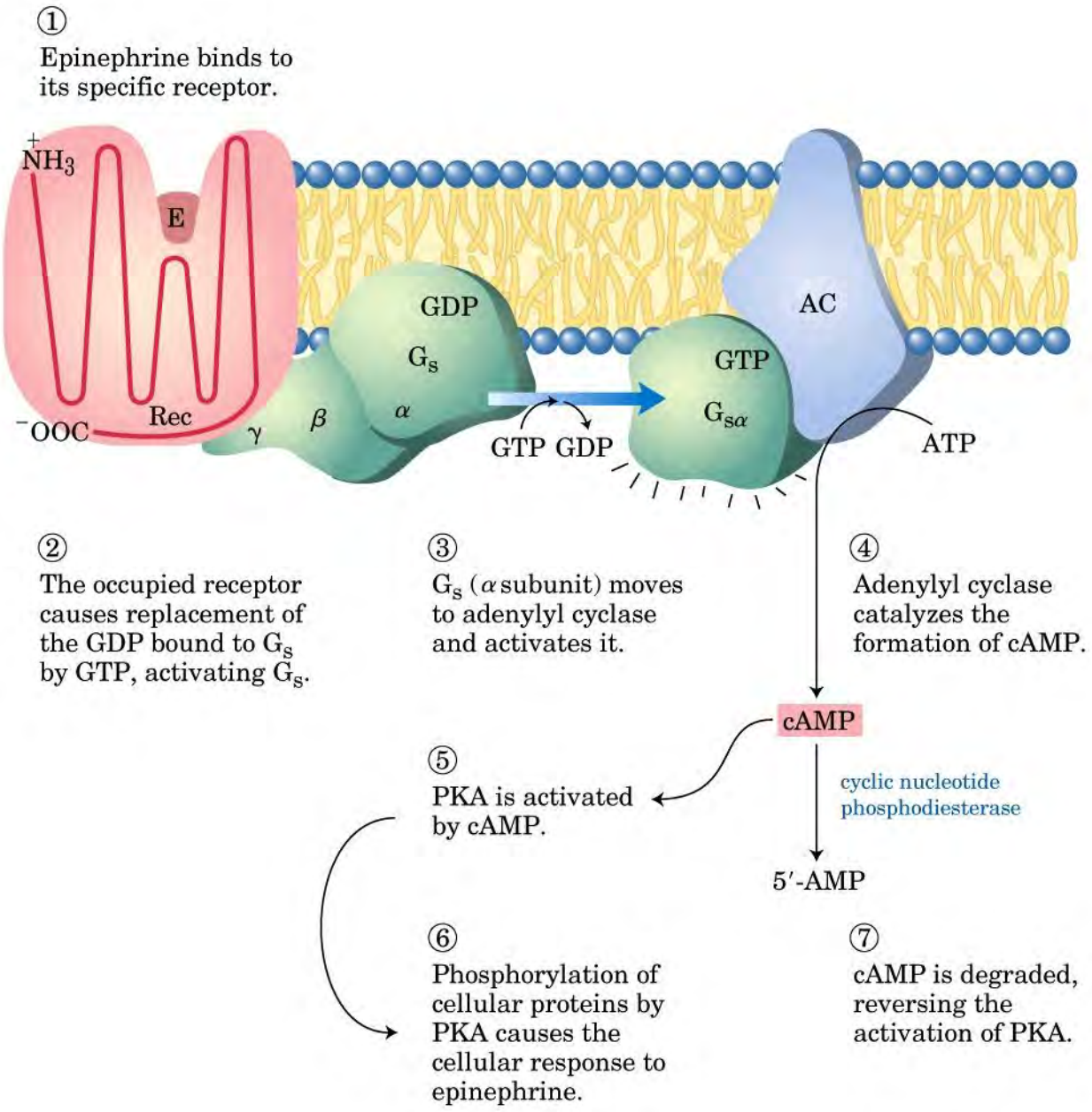
Stimulates glycolysis, inhibits gluconeogenesis



↓[Fructose 2,6-bisphosphate]

Inhibits glycolysis, stimulates gluconeogenesis


Recettore per il glucagone
Glucagone
Adenilato ciclasi
cAMP
ATP
GLUCOSIO ABBONDANTE
(glicolisi attiva)
GLUCOSIO SCARSO
(glicolisi inattiva)
Fruttosio 2,6-bisfosfato
(stimola la PFK)
Proteina chinasi A
ATP
ADP
Fruttosio 6-fosfato
(nessuna stimolazione di PFK)
PFK
PFK2
FBPasi2
ADP
ATP
Fruttosio 6-fosfato
Fosfoproteina fosfatasi
Fruttosio 2,6-bisfosfato


①
Epinephrine binds to its specific receptor.
+NH3
E
Rec
−OOC
GDP
Gs
α
β
γ
GTP GDP
GTP
Gsα
AC
ATP
②
The occupied receptor causes replacement of the GDP bound to Gs by GTP, activating Gs.
③
Gs (α subunit) moves to adenylyl cyclase and activates it.
④
Adenylyl cyclase catalyzes the formation of cAMP.
cAMP
⑤
PKA is activated by cAMP.
cyclic nucleotide phosphodiesterase
5′-AMP
⑥
Phosphorylation of cellular proteins by PKA causes the cellular response to epinephrine.
⑦
cAMP is degraded, reversing the activation of PKA.