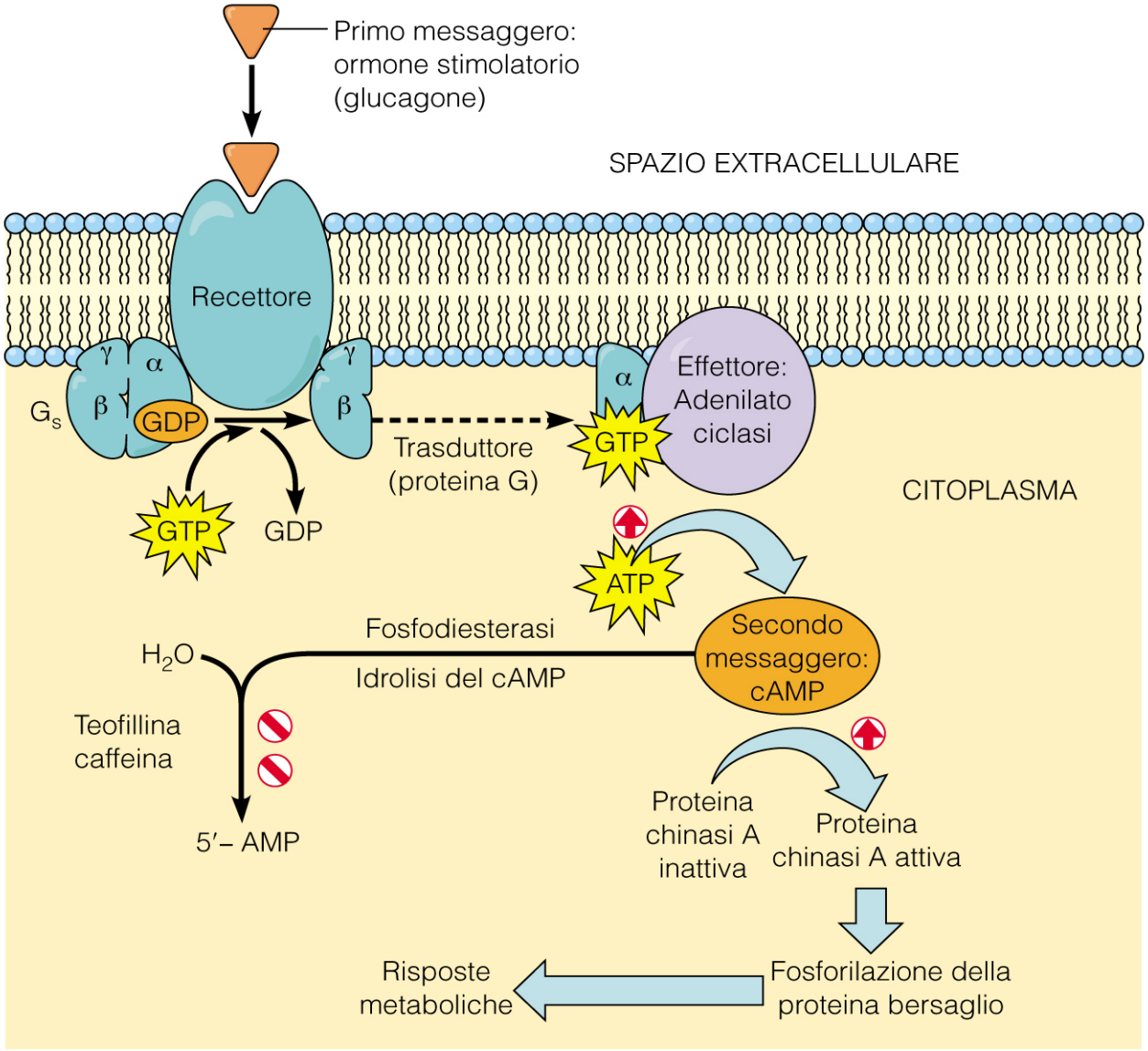
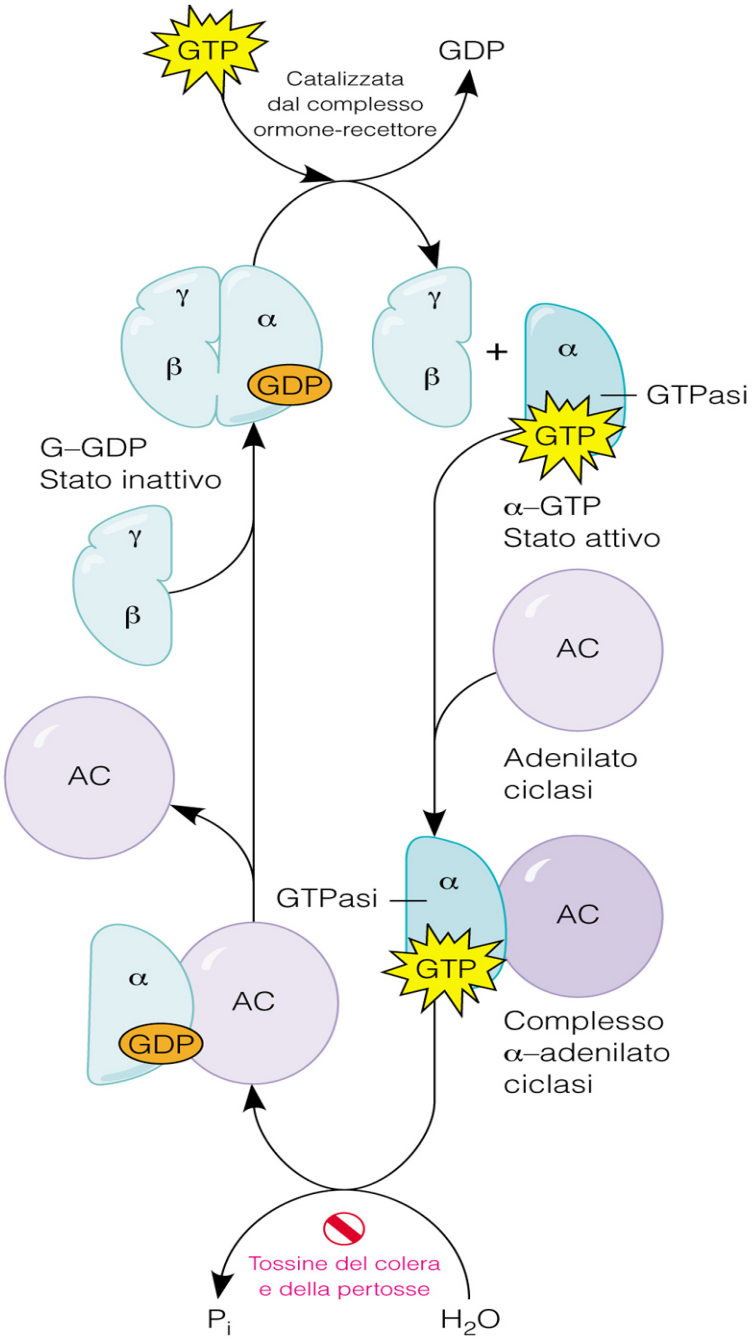
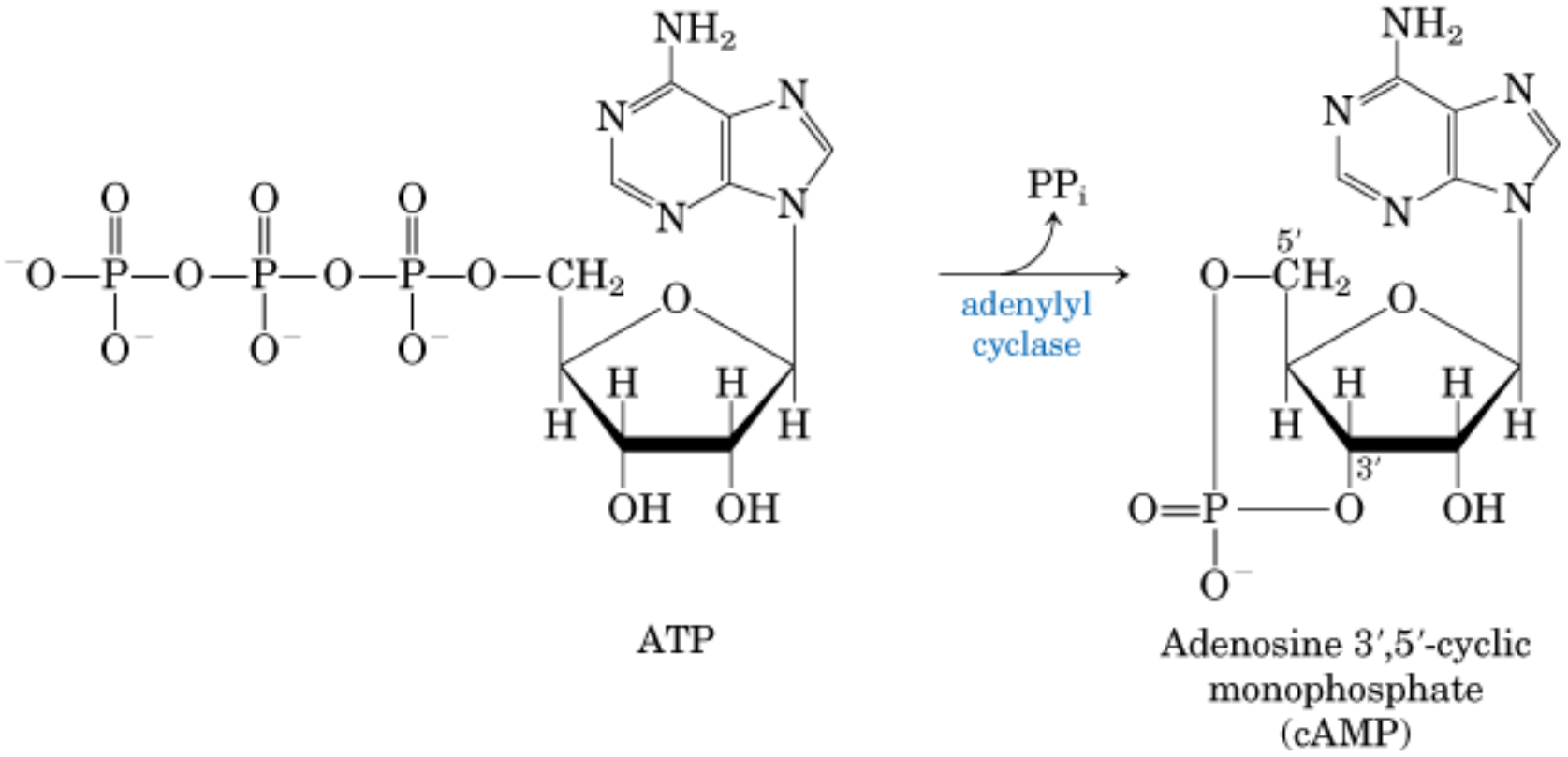


Legenda:

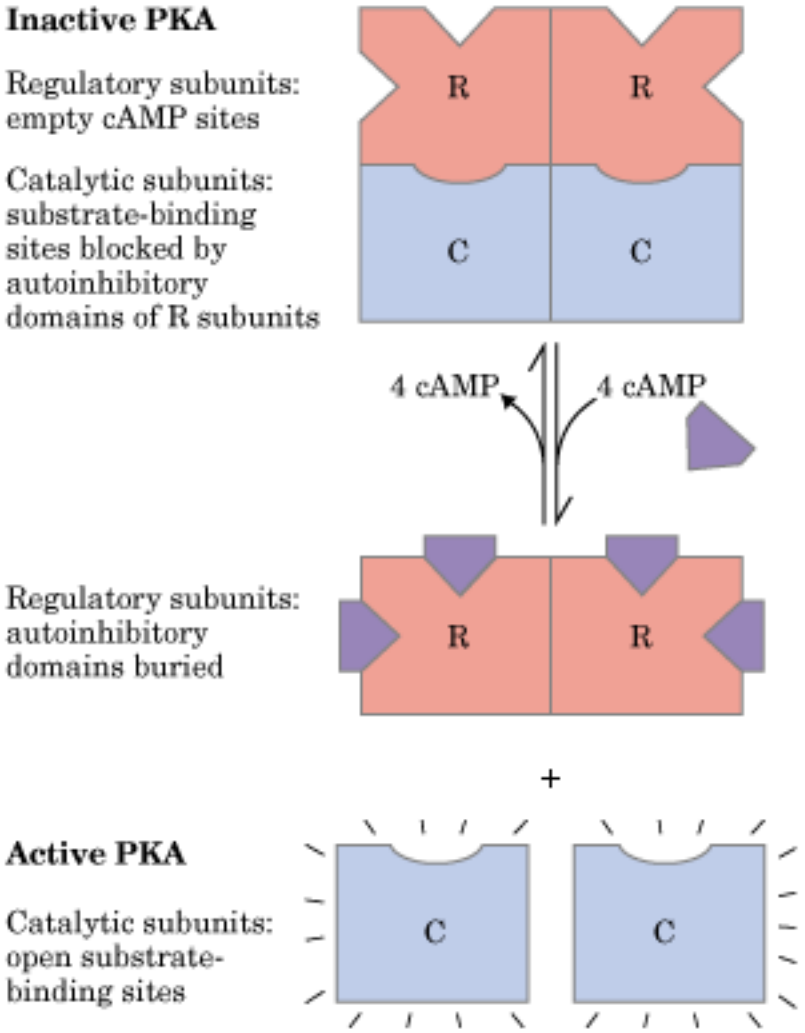
- Risposta stimolatoria
- Risposta inibitoria


GTP
GDP
Catalizzata
dal complesso
ormone-recettore
γ
α
β
GDP
+
GTPasi
GTP
G–GDP
Stato inattivo
α–GTP
Stato attivo
AC
Adenilato
ciclasi
GTPasi
Complesso
α–adenilato
ciclasi
Tossine del colera
e della pertosse
P_i
H_2O



ATP

Adenosine 3′,5′-cyclic monophosphate (cAMP)


Inactive PKA
Regulatory subunits: empty cAMP sites
Catalytic subunits: substrate-binding sites blocked by autoinhibitory domains of R subunits
R
R
C
C
4 cAMP
4 cAMP
Regulatory subunits: autoinhibitory domains buried
R
R
+
Active PKA
Catalytic subunits: open substrate-binding sites
C
C

(a)

table 13–3

Some Enzymes Regulated by cAMP-Dependent Phosphorylation (by PKA)

Enzyme	Sequence phosphorylated*	Pathway
Glycogen synthase	RASCTSSS	Glycogen synthesis
Phosphorylase *b* kinase	α subunit: VEFRRLSI β subunit: RTKRSGSV	Glycogen breakdown
Pyruvate kinase (rat liver)	GVLRRASVAZL	Glycolysis
Pyruvate dehydrogenase complex (type L)	GYLRRASV	Pyruvate to acetyl-CoA
Hormone-sensitive lipase	PMRRSV	Triacylglycerol mobilization and fatty acid oxidation
Phosphofructokinase-2/fructose 2,6-bisphosphatase	LQRRRGSSIPQ	Glycolysis/gluconeogenesis
Tyrosine hydroxylase	FIGRRQSL	Synthesis of L-DOPA, dopamine, norepinephrine, and epinephrine
Histone H1	AKRKASGPPVS	DNA condensation
Histone H2B	KKAKASRKESYSVYVYK	DNA condensation
Cardiac phospholamban (a cardiac pump regulator)	AIRRAST	Regulation of intracellular [Ca^{2+}]
Protein phosphatase-1 inhibitor-1	IRRRRPTP	Regulation of protein dephosphorylation
CREB	ILSRRPSY	cAMP regulation of gene expression
PKA consensus sequence†	XR(R/K)X(S/T)B	

*The phosphorylated S or T residue is shown in red. All residues are given as their one-letter abbreviations (see Table 5–1).

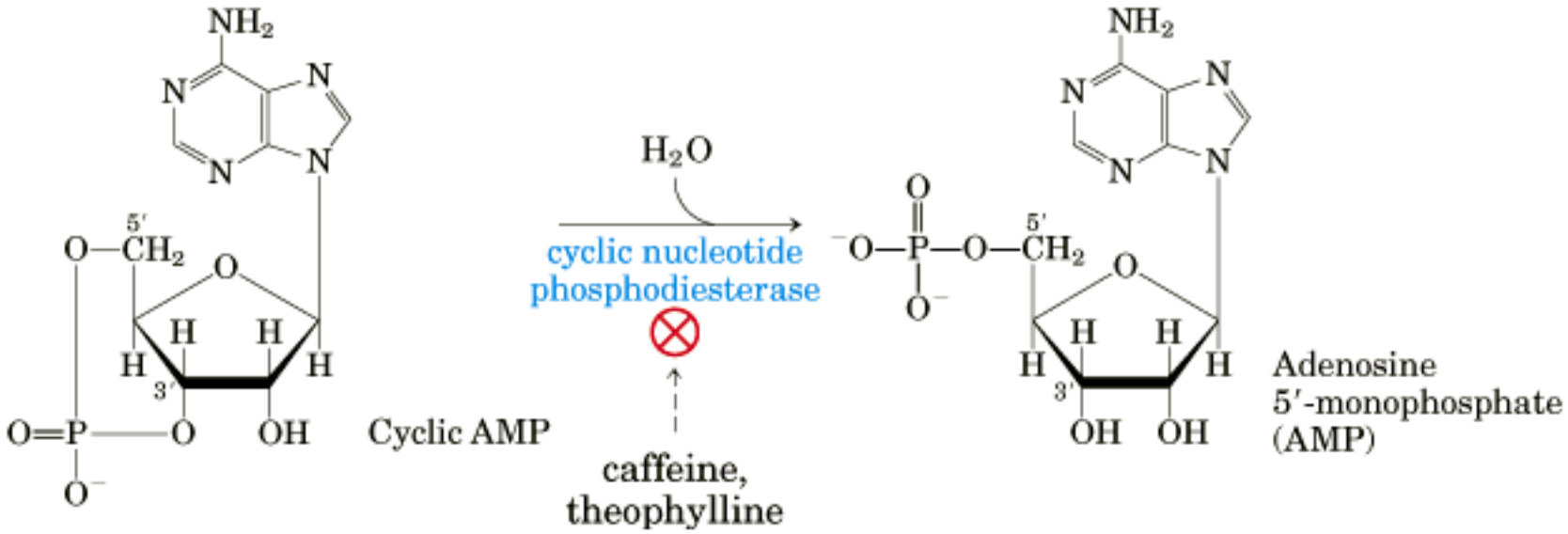
†X is any amino acid; B is any hydrophobic amino acid.

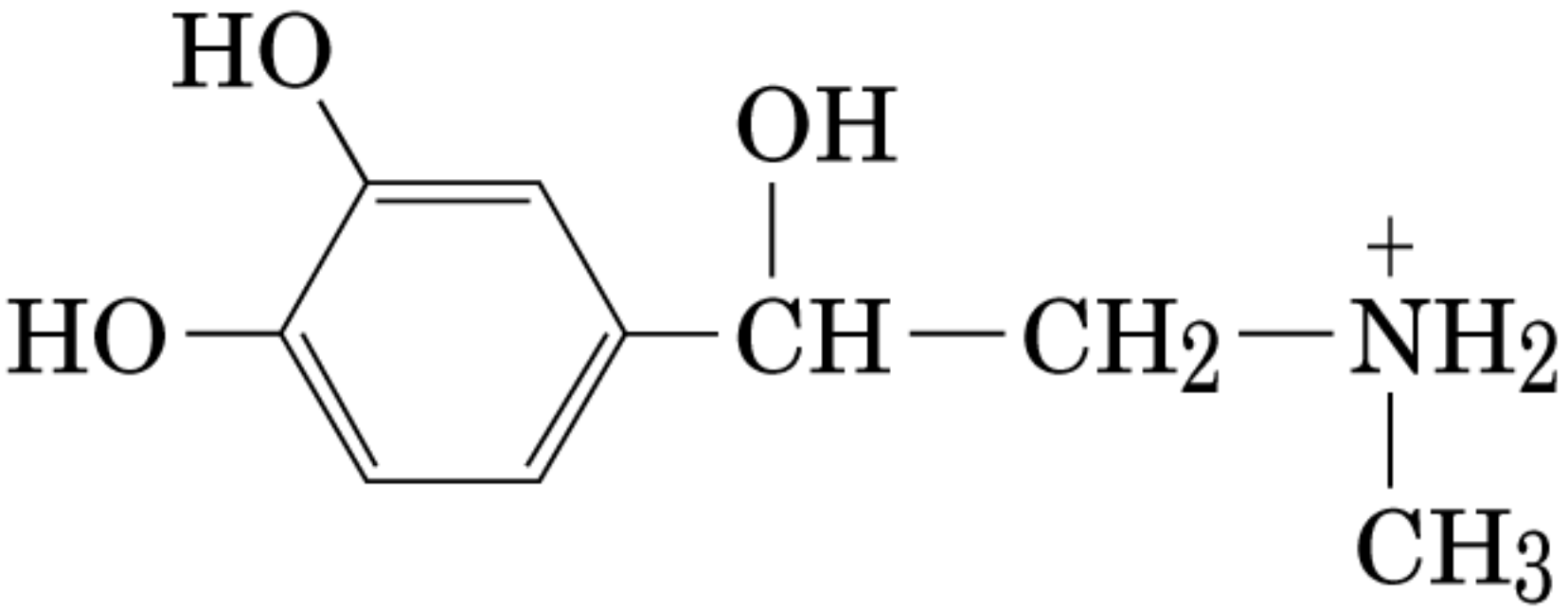
table 13–4

Some Signals That Use cAMP as Second Messenger

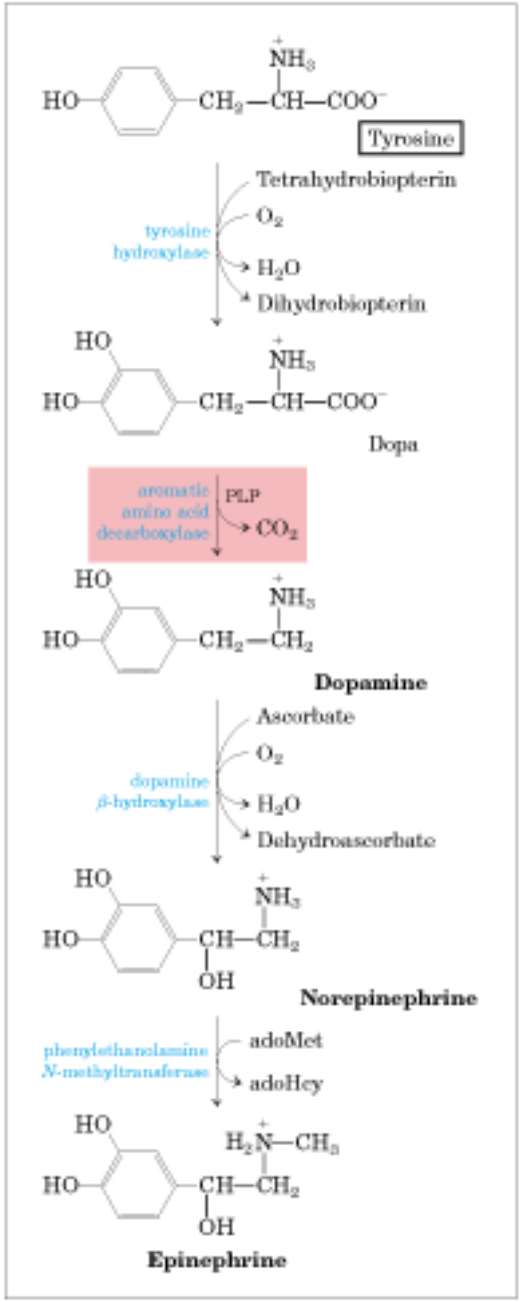
Corticotropin (ACTH)
Corticotropin-releasing hormone (CRH)
Dopamine [D-1, D-2]*
Epinephrine (β-adrenergic)
Follicle-stimulating hormone (FSH)
Glucagon
Histamine [H-2]*
Luteinizing hormone (LH)
Melanocyte-stimulating hormone (MSH)
Odorants (many)
Parathyroid hormone
Prostaglandins E_1, E_2 (PGE_1, PGE_2)
Serotonin [5-HT-1α, 5-HT-2]*
Somatostatin
Tastants (sweet, bitter)
Thyroid-stimulating hormone (TSH)

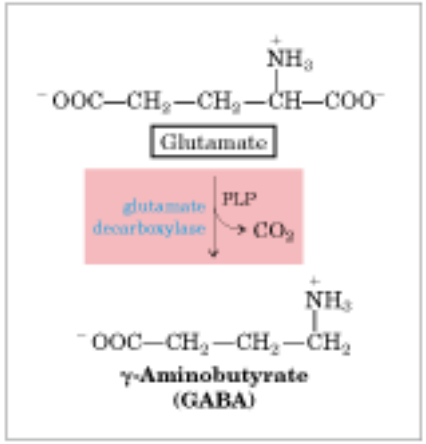
*Some signals have two or more receptor subtypes (shown in square brackets), which may have different transduction mechanisms. For example, serotonin is detected in some tissues by receptor subtypes 5-HT-1a and 5-HT-1b, which act through adenylyl cyclase and cAMP, and in other tissues by receptor subtype 5-HT-1c, acting through the phospholipase C–IP_3 mechanism (see Table 13–5).

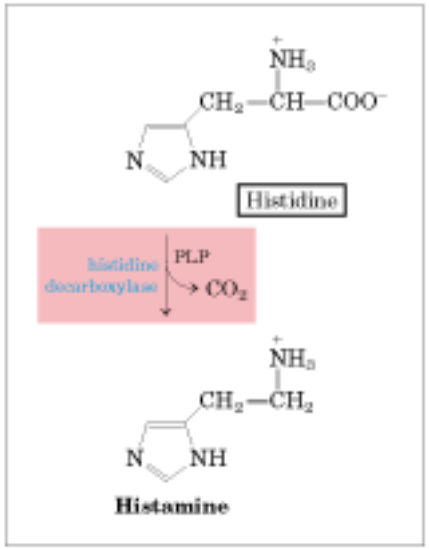

NH2
N
N
N
N
5′
O—CH2
O
H
H
H
H
3′
O=P—O
OH
O⁻
Cyclic AMP
H2O
cyclic nucleotide
phosphodiesterase
caffeine,
theophylline
NH2
N
N
N
N
O
⁻O—P—O—CH2
O⁻
5′
O
H
H
H
H
3′
OH
OH
Adenosine
5′-monophosphate
(AMP)

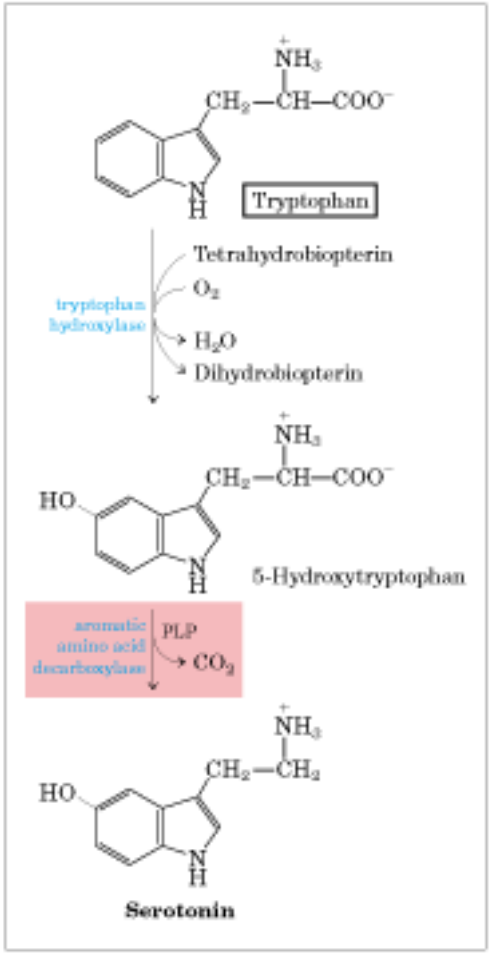


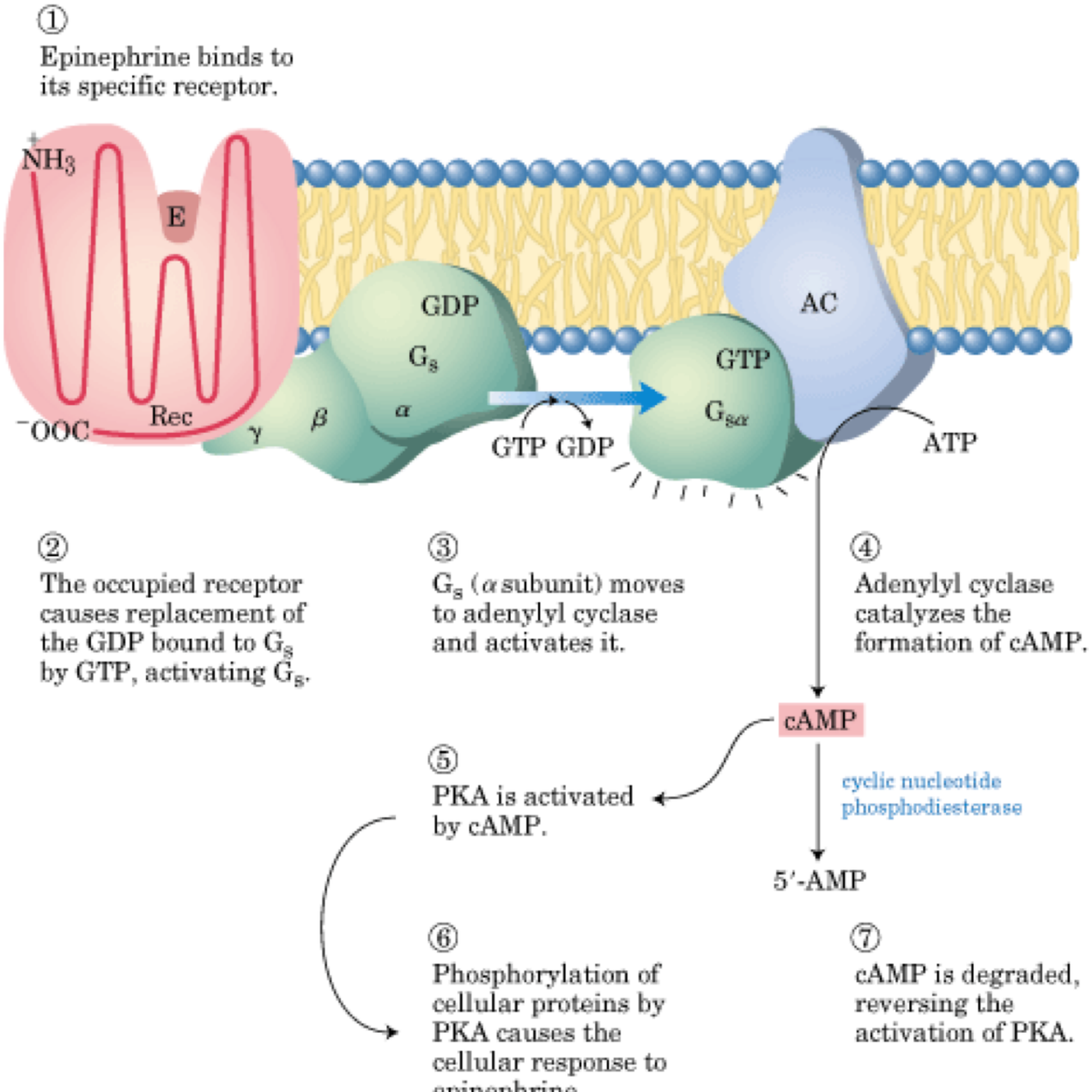
Epinephrine

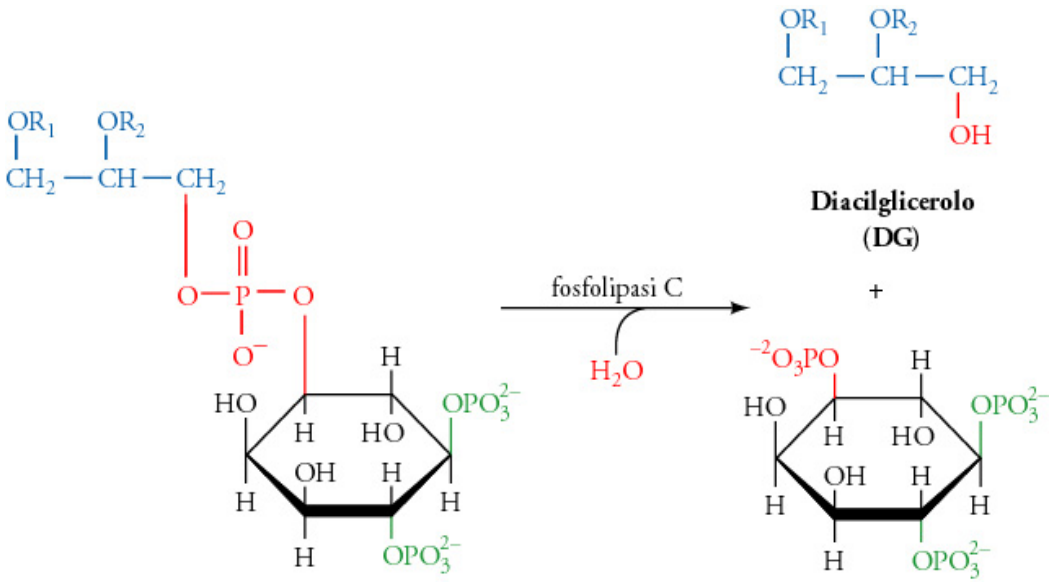

Tyrosine
Tetrahydrobiopterin
tyrosine hydroxylase
O2
H2O
Dihydrobiopterin
Dopa
aromatic amino acid decarboxylase
PLP
CO2
Dopamine
Ascorbate
dopamine β-hydroxylase
Dehydroascorbate
Norepinephrine
phenylethanolamine N-methyltransferase
adoMet
adoHcy
Epinephrine


Glutamate
glutamate decarboxylase
PLP
CO2
γ-Aminobutyrate (GABA)


Histidine
histidine decarboxylase
PLP
CO2
Histamine

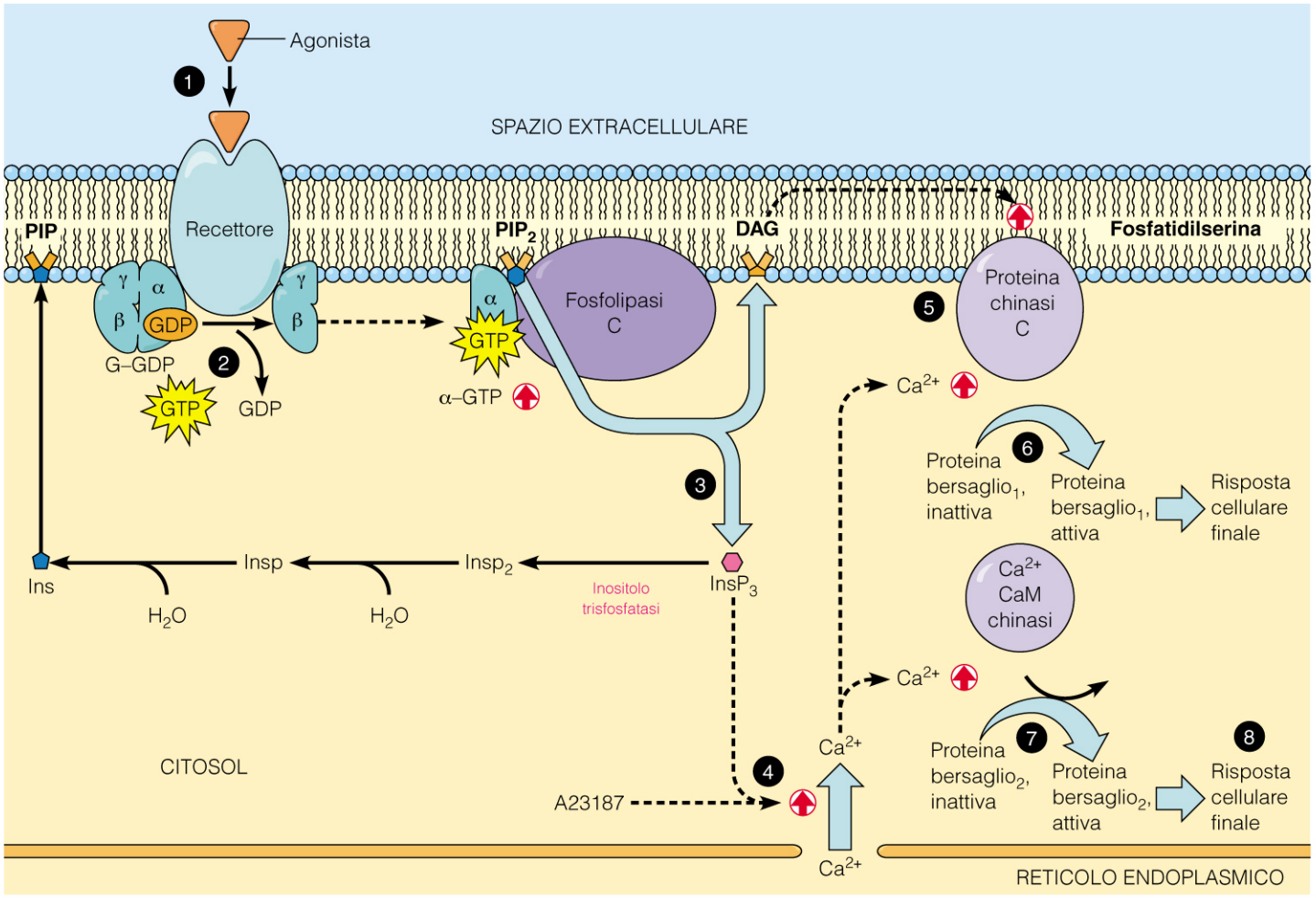

Tryptophan
Tetrahydrobiopterin
tryptophan hydroxylase
O2
H2O
Dihydrobiopterin
5-Hydroxytryptophan
aromatic amino acid decarboxylase
PLP
CO2
Serotonin


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.



Fosfatidilinositolo-4,5-bisfosfato (PIP_2)

Inositolo-1,4,5-trisfosfato (IP_3)


Agonista
1
SPAZIO EXTRACELLULARE
Recettore
PIP
PIP2
DAG
Fosfatidilserina
γ
α
β
GDP
G–GDP
2
GTP
GDP
α
GTP
α–GTP
Fosfolipasi C
5
Proteina chinasi C
Ca2+
Proteina bersaglio1, inattiva
6
Proteina bersaglio1, attiva
Risposta cellulare finale
3
Ins
Insp
Insp2
InsP3
H2O
H2O
Inositolo trisfosfatasi
Ca2+ CaM chinasi
Ca2+
CITOSOL
4
A23187
Ca2+
Ca2+
Proteina bersaglio2, inattiva
7
Proteina bersaglio2, attiva
8
Risposta cellulare finale
RETICOLO ENDOPLASMICO

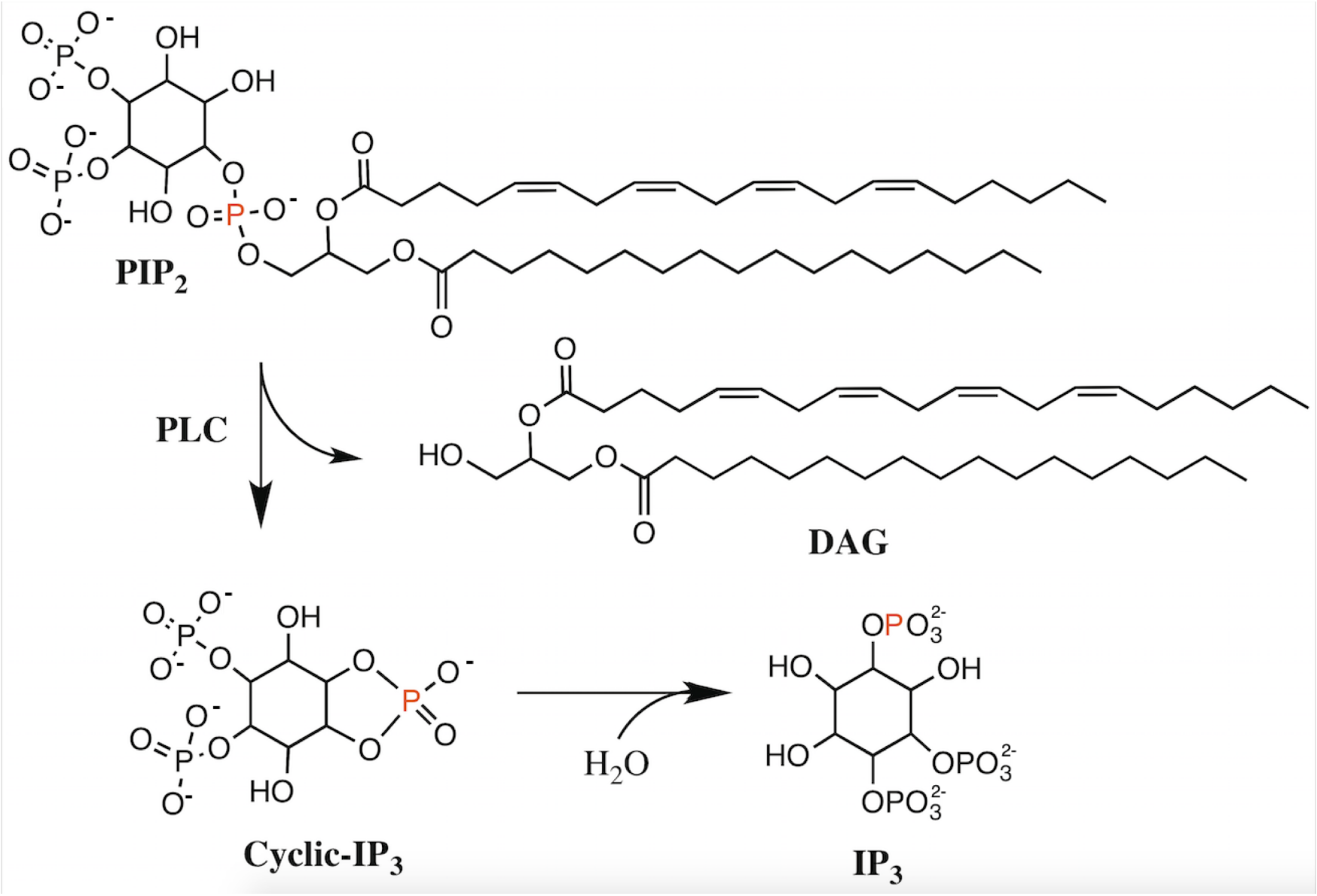
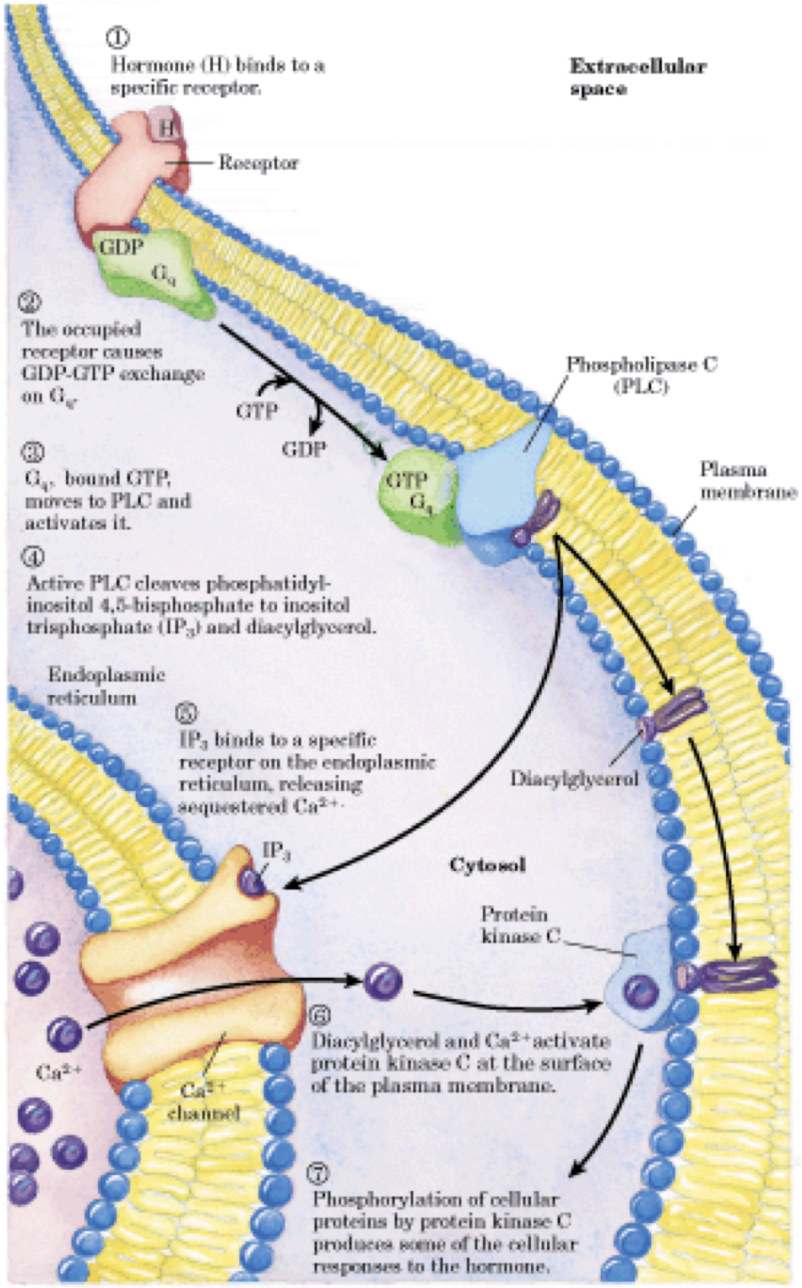

PIP2
PLC
DAG
Cyclic-IP3
H2O
IP3

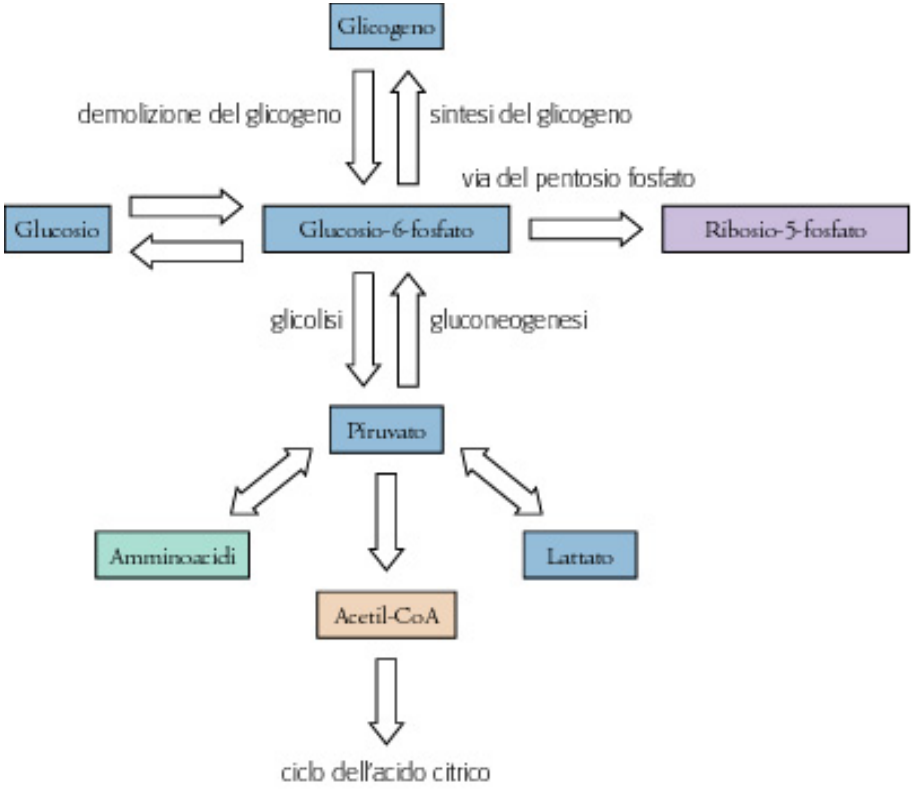
table 13–5

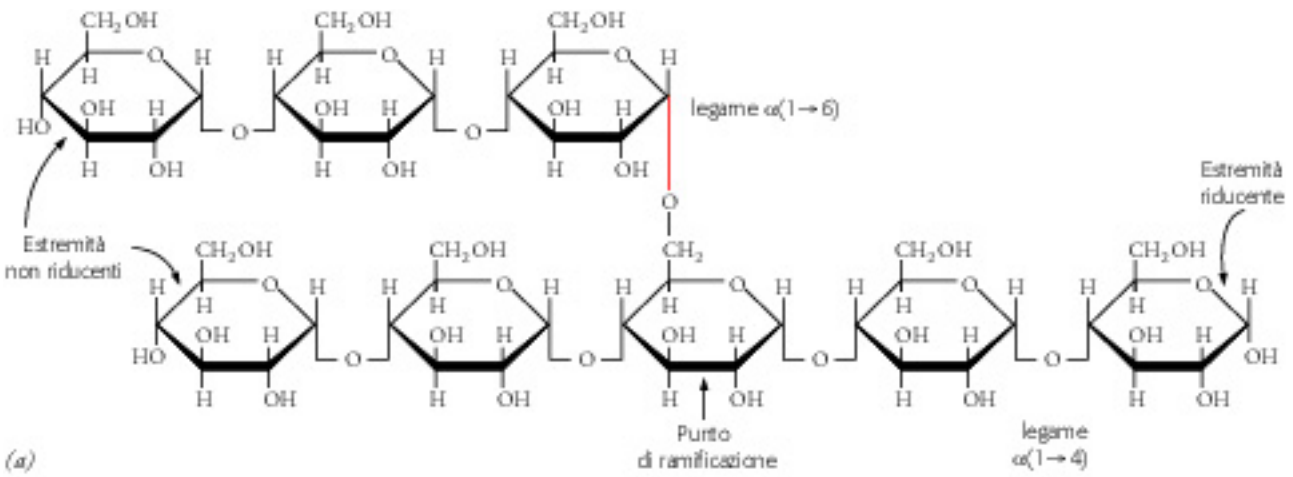
Some Signals That Act through Phospholipase C and IP_3

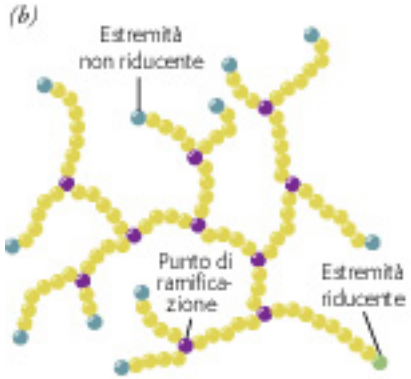
Acetylcholine [muscarinic M_1]
α_1-Adrenergic agonists
Angiogenin
Angiotensin II
ATP [P_{2x} and P_{2y}]*
Auxin
Gastrin-releasing peptide
Glutamate
Gonadotropin-releasing hormone (GRH)
Histamine [H_1]*
Light (*Drosophila*)
Oxytocin
Platelet-derived growth factor (PDGF)
Serotonin [5-HT-1c]*
Thyrotropin-releasing hormone (TRH)
Vasopressin

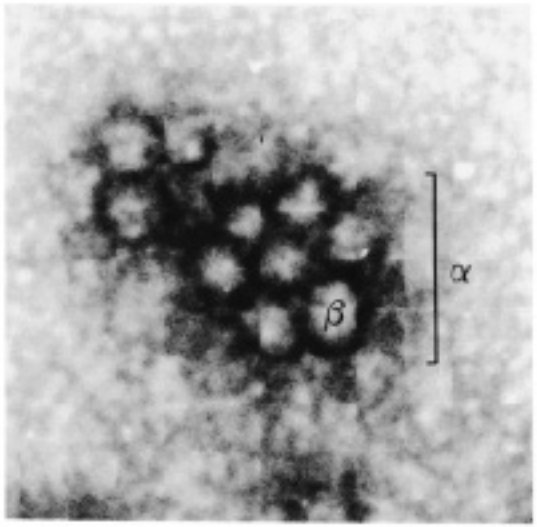
*Receptor subtypes are in square brackets; see footnote to Table 13–4.

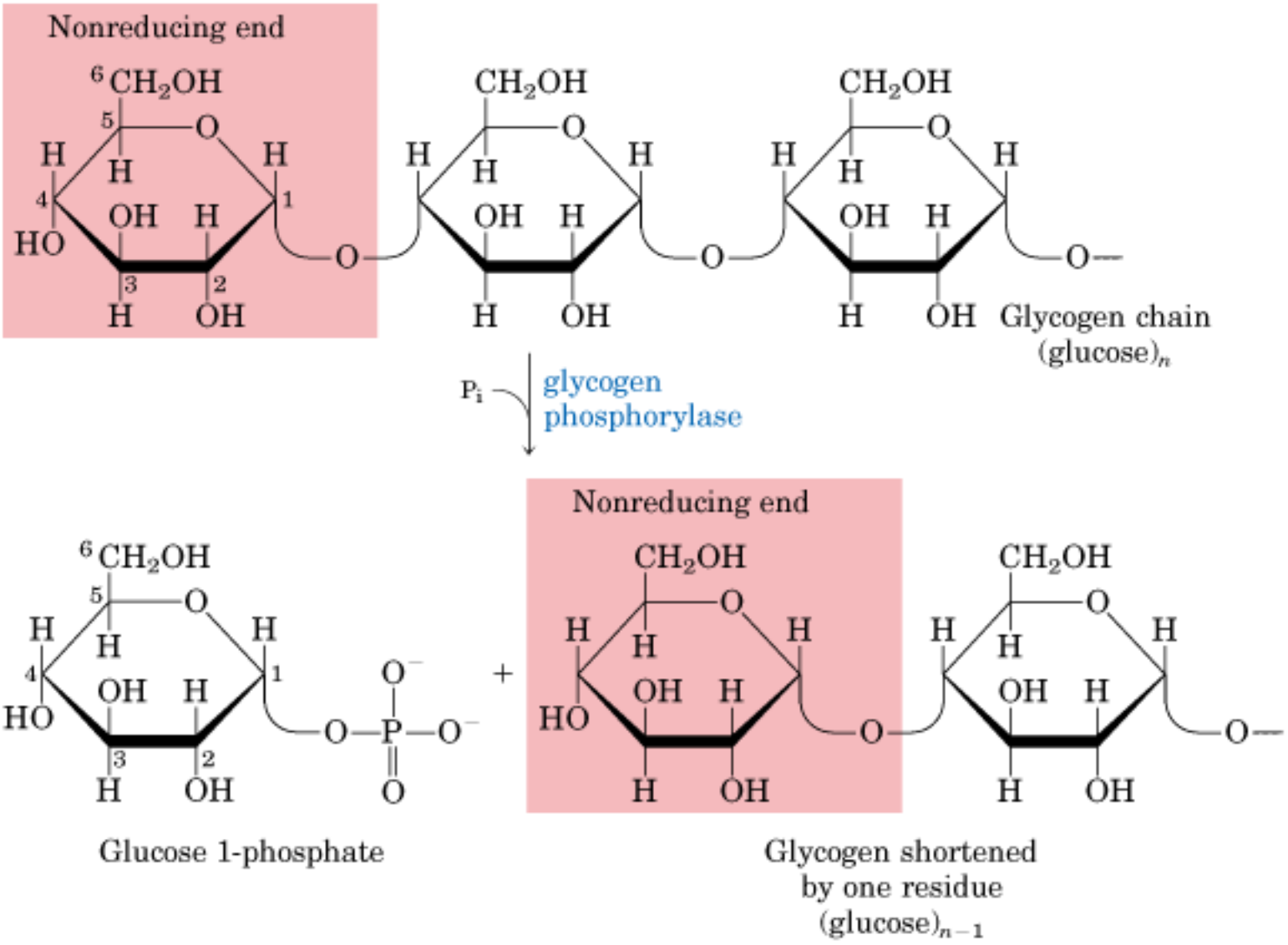

① Hormone (H) binds to a specific receptor.
Extracellular space
H
Receptor
GDP
G_q
② The occupied receptor causes GDP-GTP exchange on G_q.
GTP
GDP
Phospholipase C (PLC)
③ G_q, bound GTP, moves to PLC and activates it.
GTP
G_q
Plasma membrane
④ Active PLC cleaves phosphatidyl-inositol 4,5-bisphosphate to inositol trisphosphate (IP_3) and diacylglycerol.
Endoplasmic reticulum
⑤ IP_3 binds to a specific receptor on the endoplasmic reticulum, releasing sequestered Ca^{2+}.
Diacylglycerol
IP_3
Cytosol
Protein kinase C
⑥ Diacylglycerol and Ca^{2+} activate protein kinase C at the surface of the plasma membrane.
Ca^{2+}
Ca^{2+} channel
⑦ Phosphorylation of cellular proteins by protein kinase C produces some of the cellular responses to the hormone.


Glicogeno
demolizione del glicogeno
sintesi del glicogeno
via del pentosio fosfato
Glucosio
Glucosio-6-fosfato
Ribosio-5-fosfato
glicolisi
gluconeogenesi
Piruvato
Amminoacidi
Lattato
Acetil-CoA
ciclo dell'acido citrico

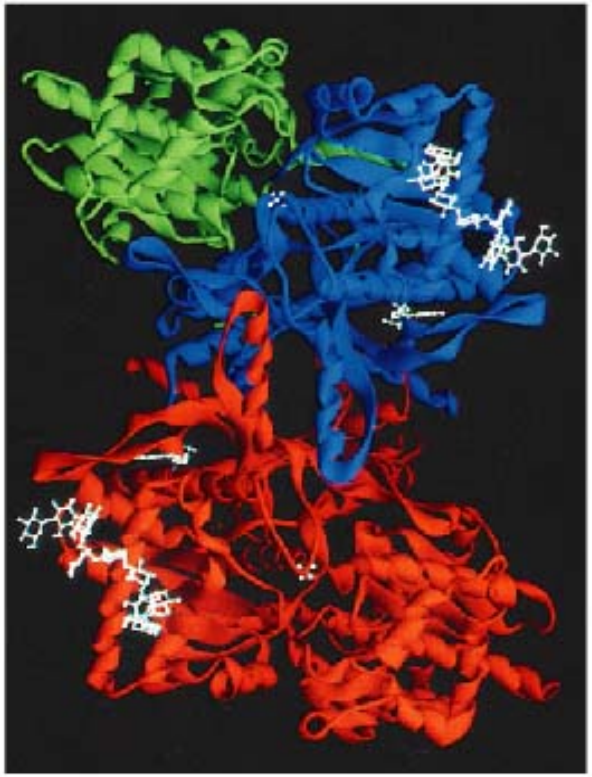

legame α(1→6)
Estremità riducente
Estremità non riducenti
Punto di ramificazione
legame α(1→4)
(a)


(b)
Estremità non riducente
Punto di ramifica-zione
Estremità riducente

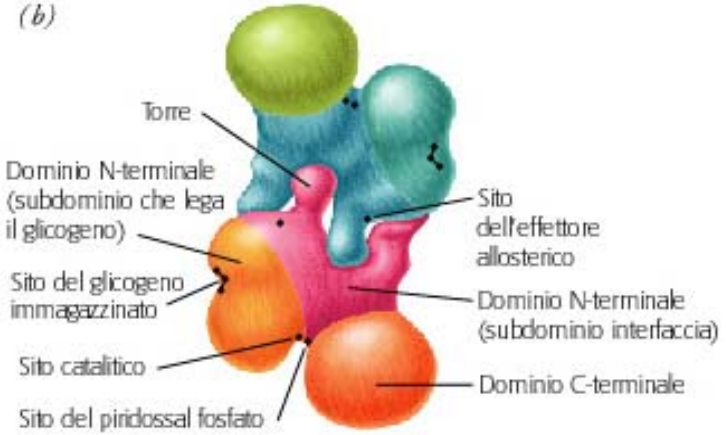

(c)
α
β

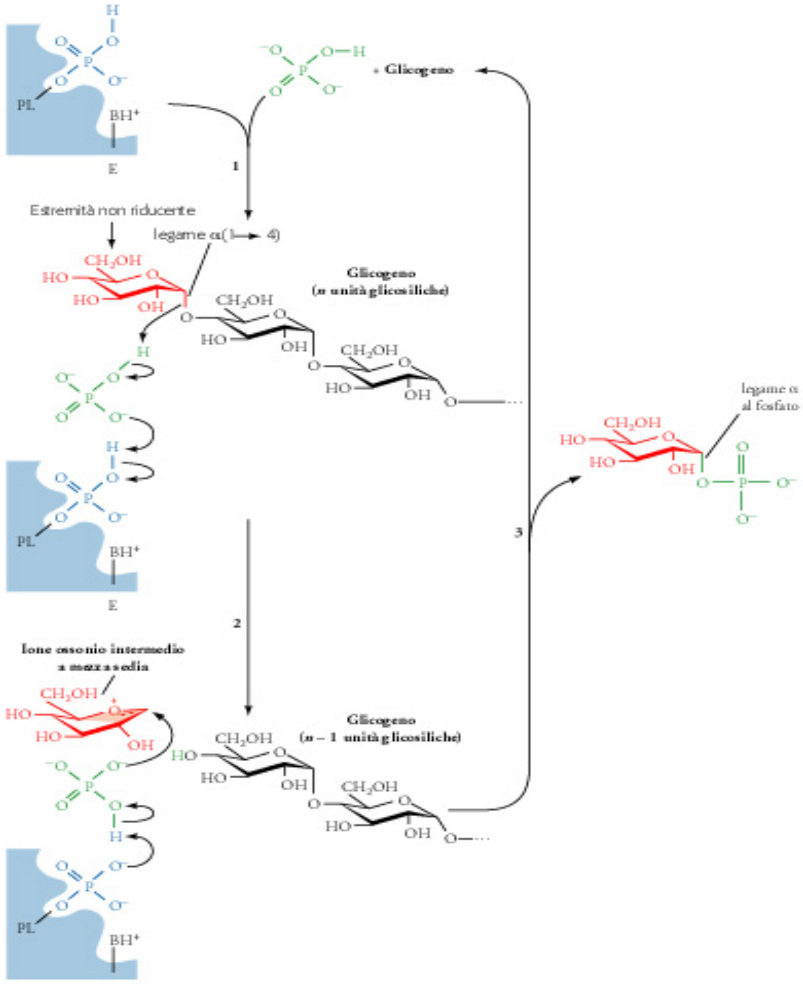

Nonreducing end
Glycogen chain
(glucose)n
Pi
glycogen
phosphorylase
Nonreducing end
Glucose 1-phosphate
Glycogen shortened
by one residue
(glucose)n−1

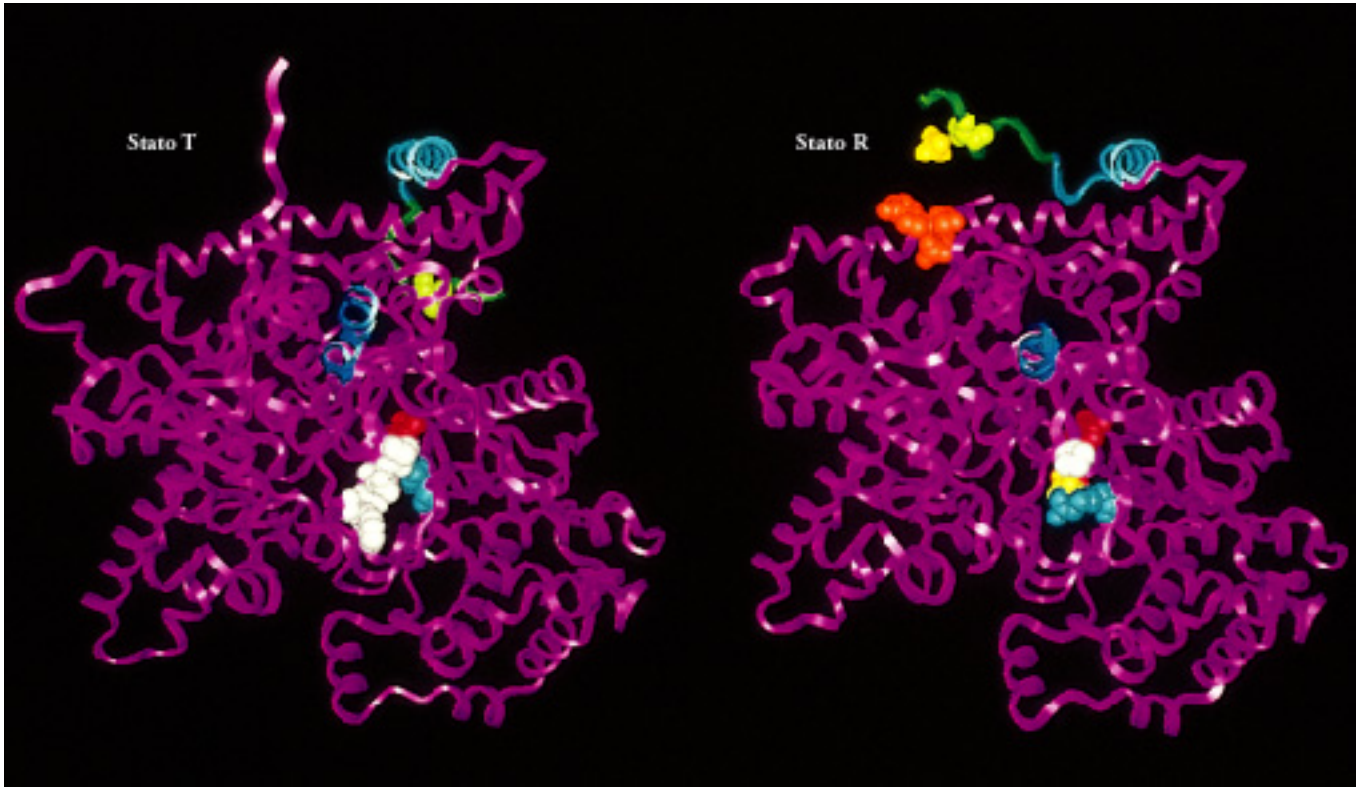
(a)

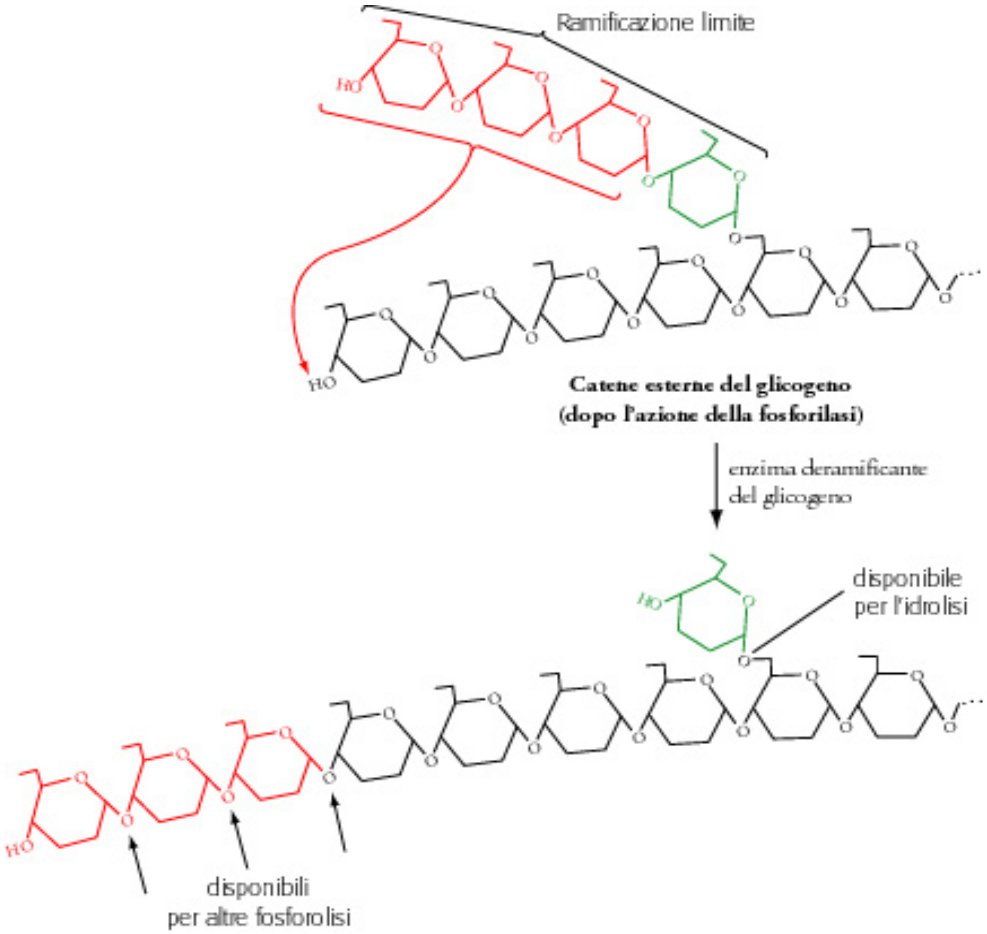


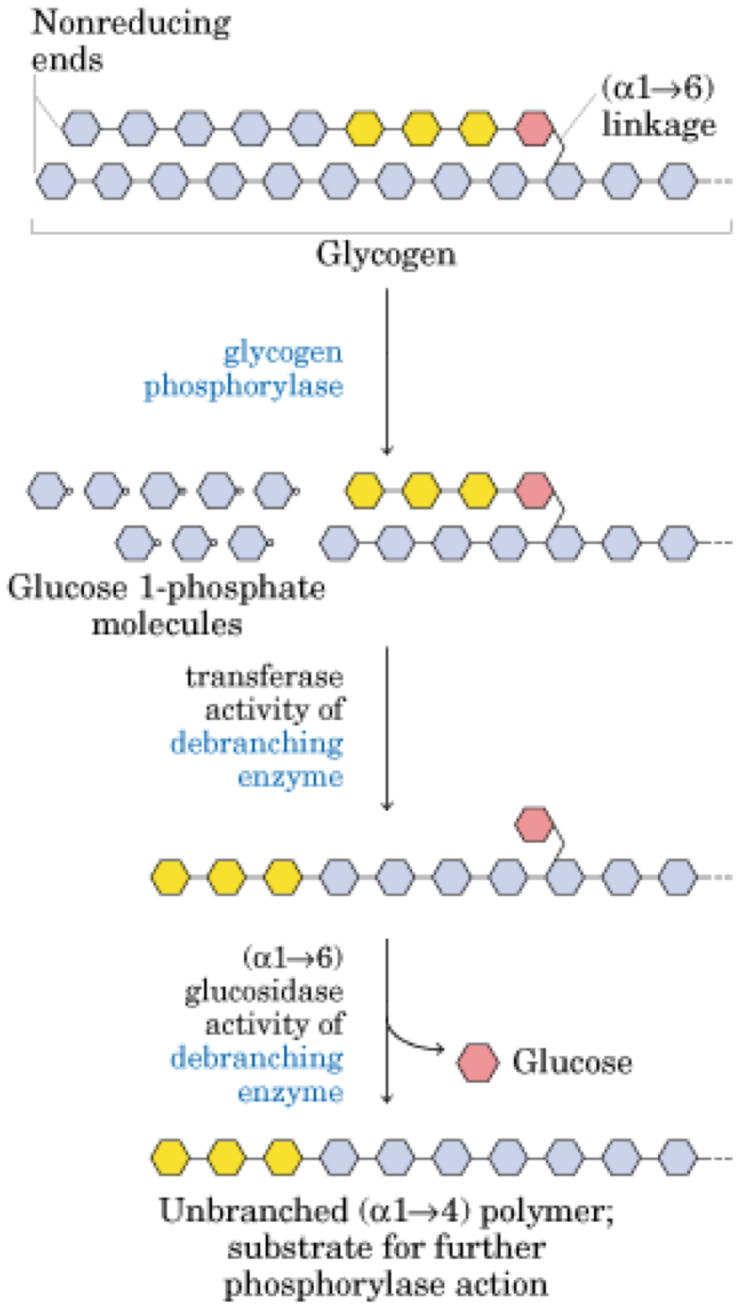
(b)

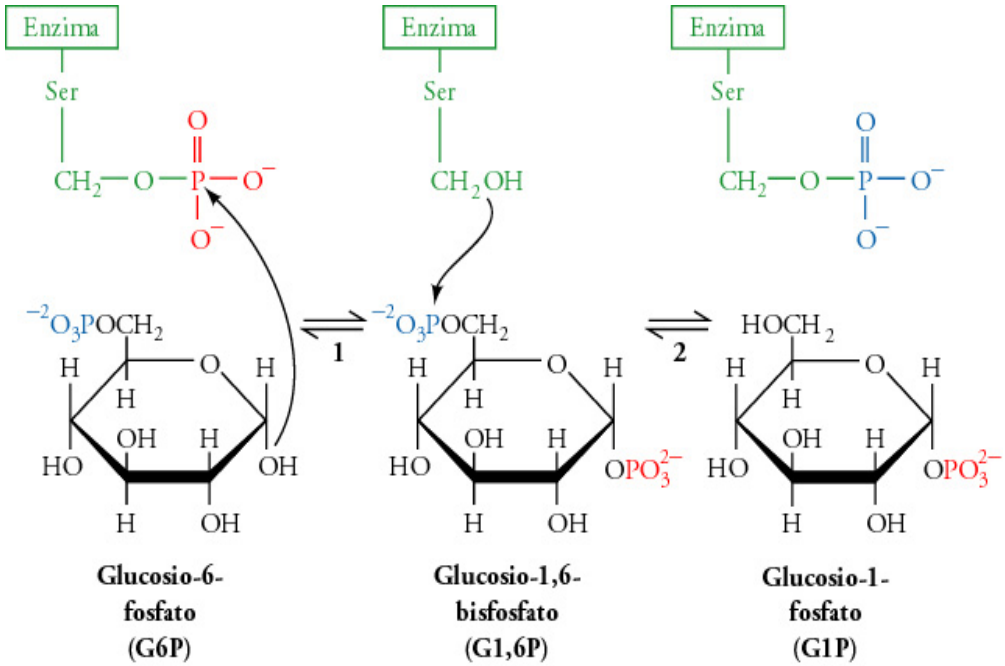

Torre
Dominio N-terminale (subdominio che lega il glicogeno)
Sito del glicogeno immagazzinato
Sito catalitico
Sito del piridossal fosfato
Sito dell'effettore allosterico
Dominio N-terminale (subdominio interfaccia)
Dominio C-terminale

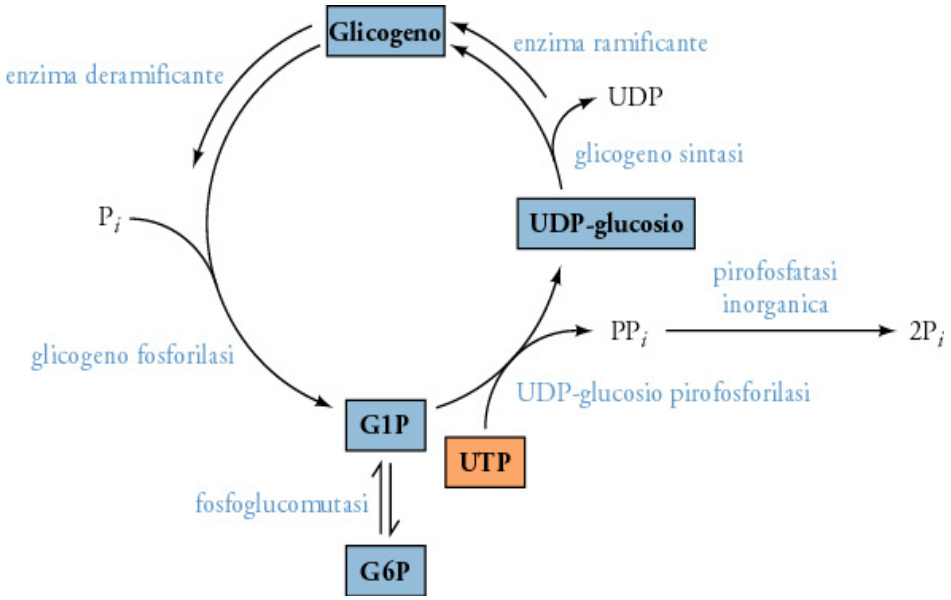

+ Glicogeno
1
Estremità non riducente
legame α(1→4)
Glicogeno
(n unità glicosiliche)
2
Ione ossonio intermedio
a mezza sedia
Glicogeno
(n – 1 unità glicosiliche)
3
legame α
al fosfato
PL
BH+
E

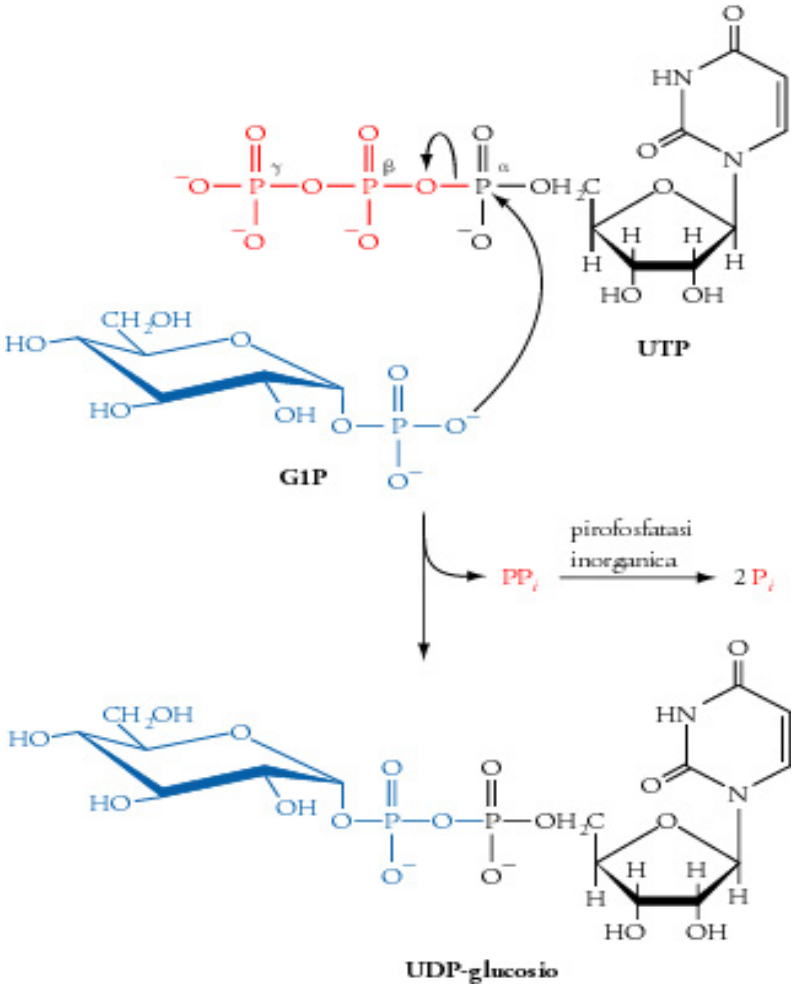

Stato T
Stato R

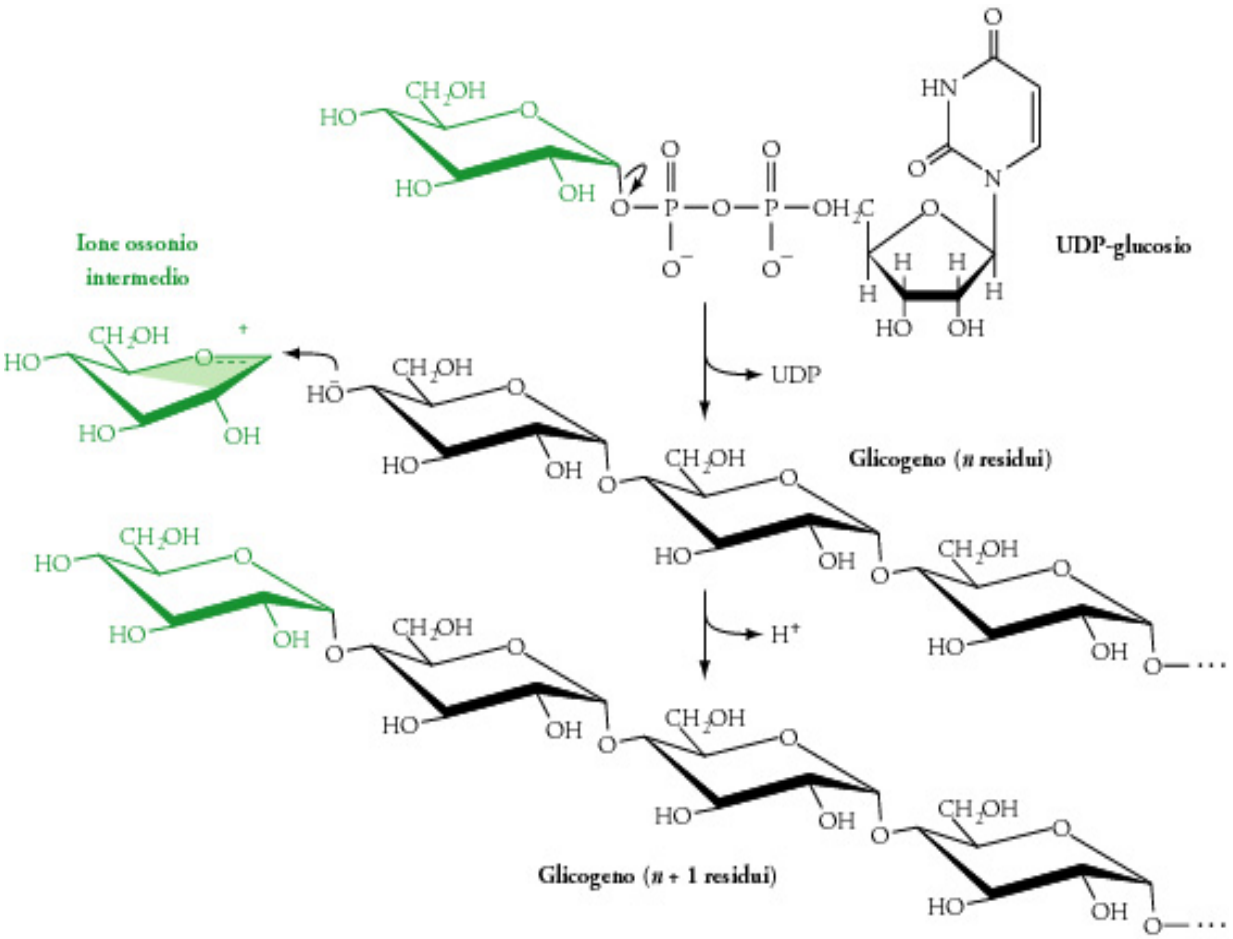

Ramificazione limite
HO
Catene esterne del glicogeno
(dopo l'azione della fosforilasi)
enzima deramificante
del glicogeno
HO
disponibile
per l'idrolisi
HO
disponibili
per altre fosforolisi

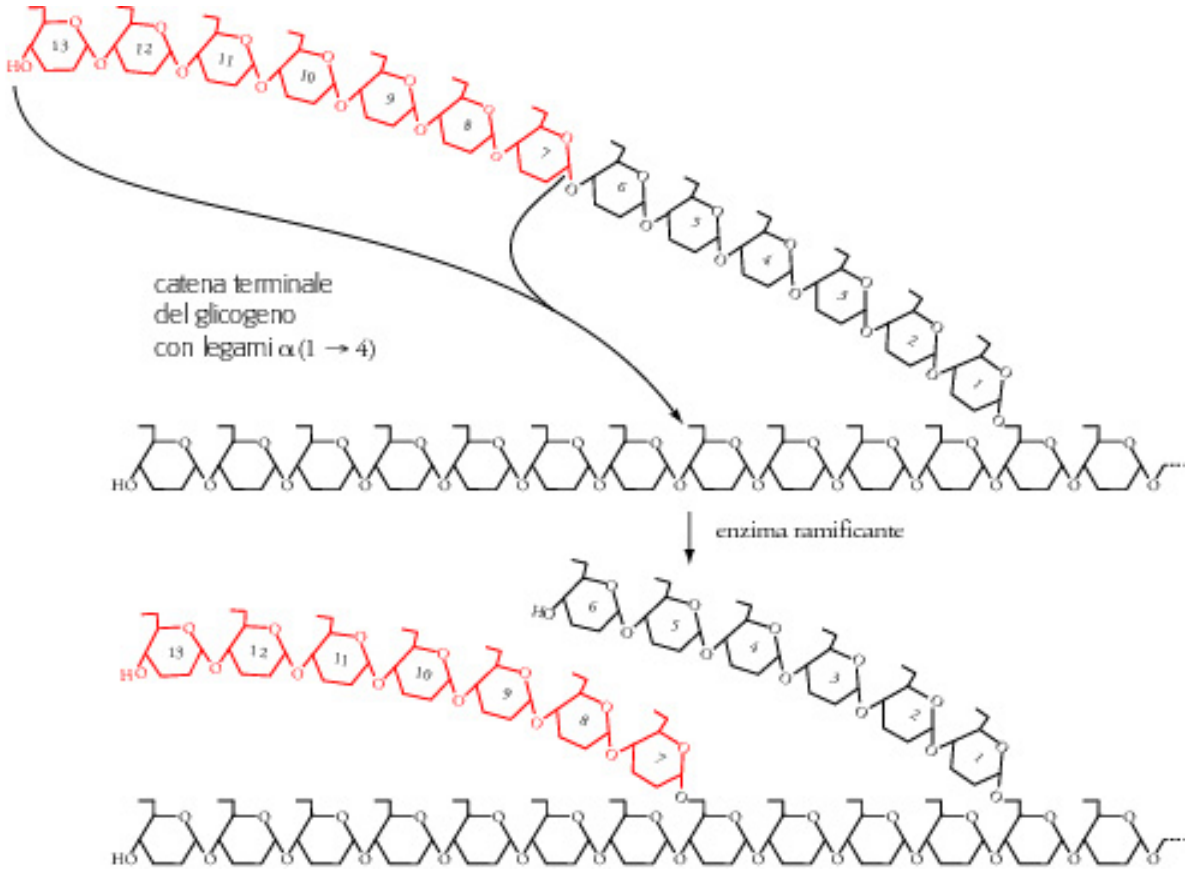

Nonreducing ends
(α1→6) linkage
Glycogen
glycogen phosphorylase
Glucose 1-phosphate molecules
transferase activity of debranching enzyme
(α1→6) glucosidase activity of debranching enzyme
Glucose
Unbranched (α1→4) polymer; substrate for further phosphorylase action

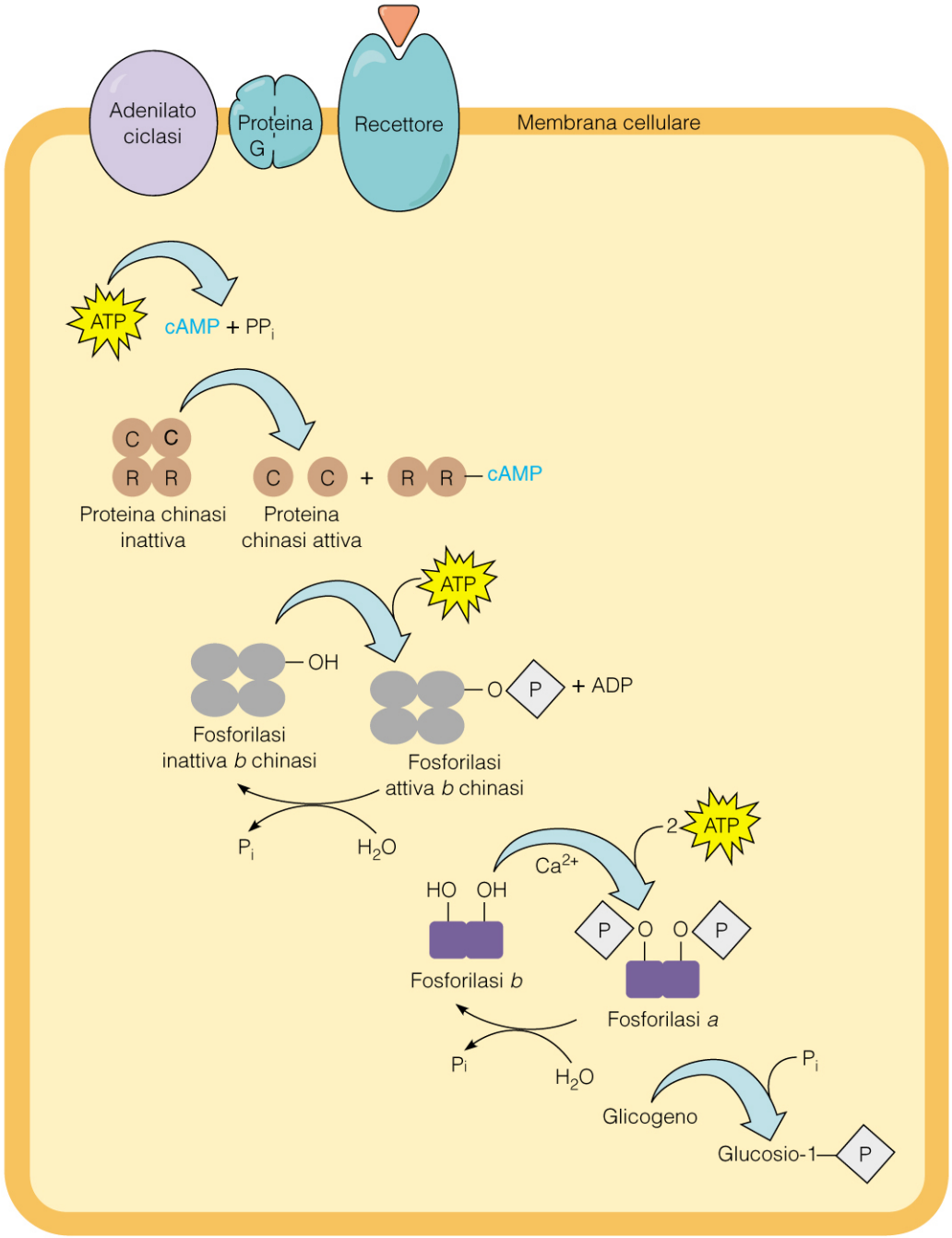

Enzima
Ser
Enzima
Ser
Enzima
Ser
1
2
Glucosio-6-fosfato (G6P)
Glucosio-1,6-bisfosfato (G1,6P)
Glucosio-1-fosfato (G1P)

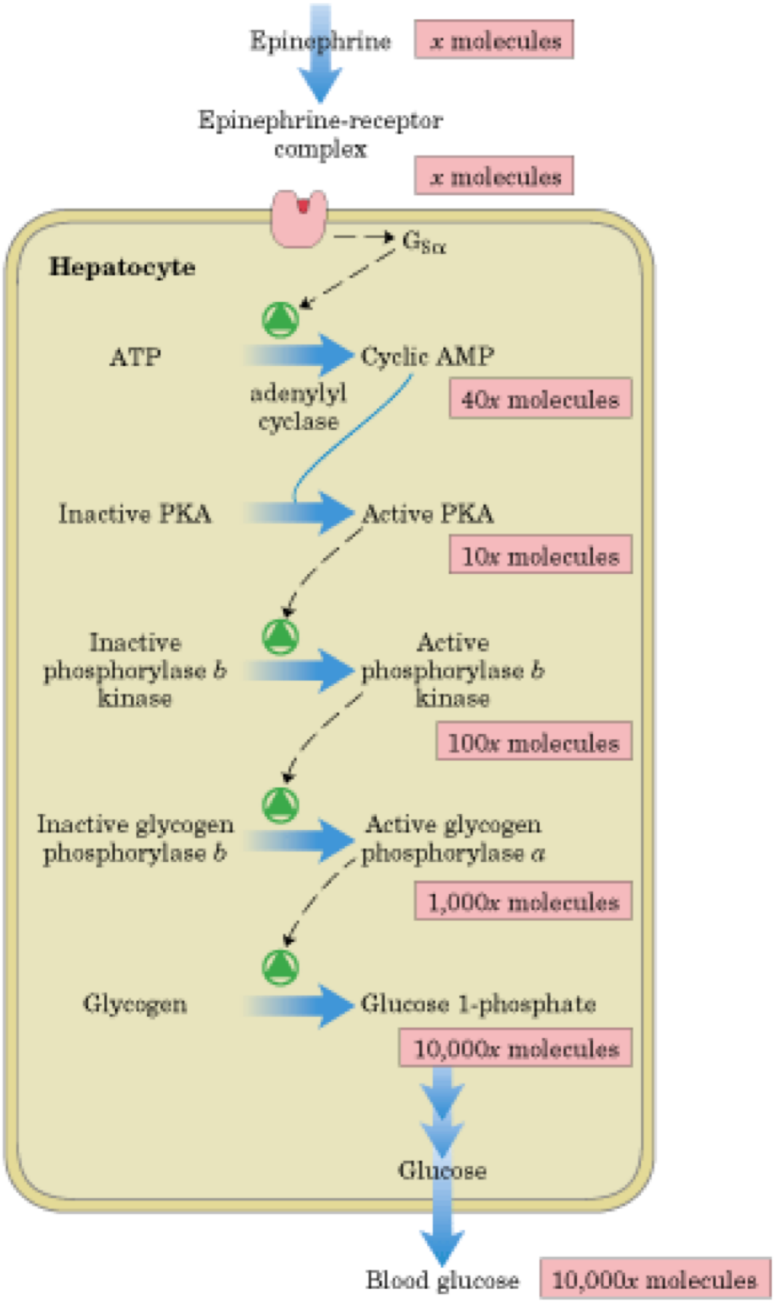

Glicogeno
enzima ramificante
enzima deramificante
UDP
glicogeno sintasi
P_i
UDP-glucosio
pirofosfatasi
inorganica
PP_i
$2P_i$
glicogeno fosforilasi
UDP-glucosio pirofosforilasi
G1P
UTP
fosfoglucomutasi
G6P

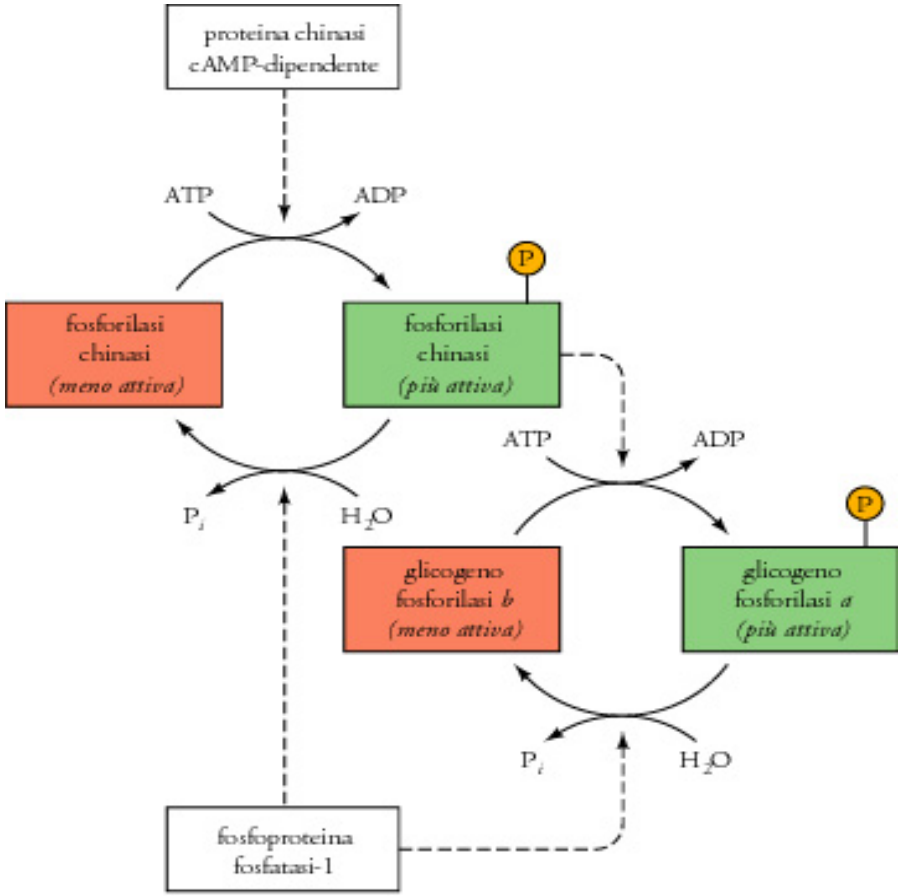

UTP
G1P
pirofosfatasi
inorganica
PP_i
$2\,P_i$
UDP-glucosio

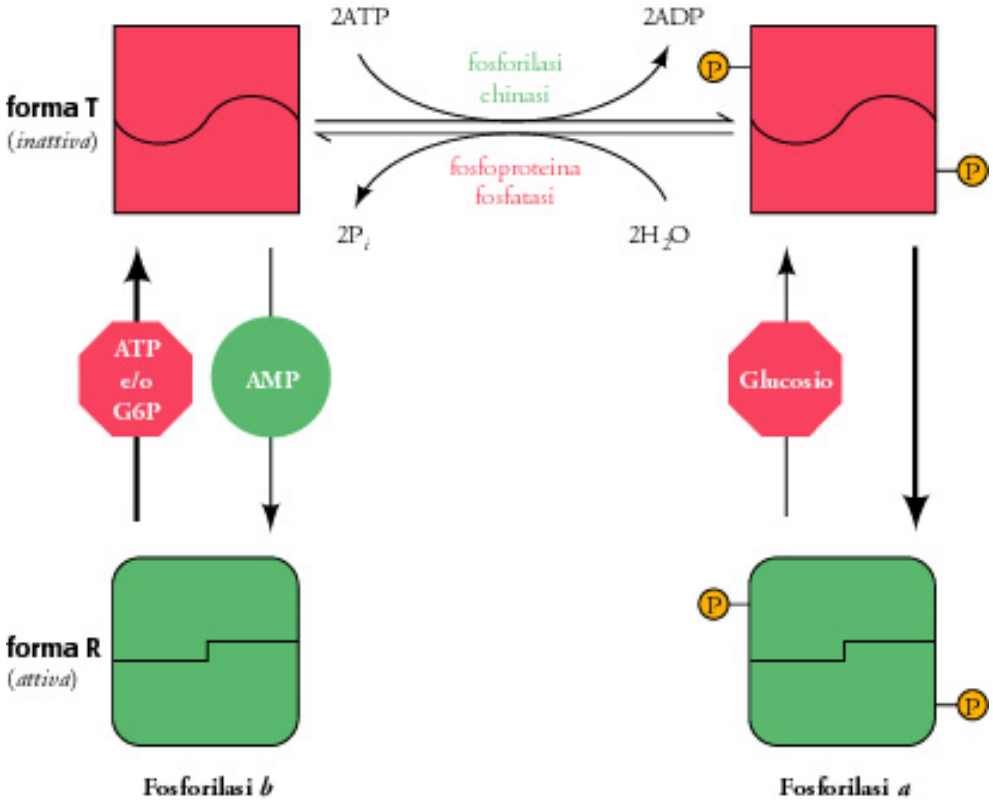

Ione ossonio intermedio
UDP-glucosio
UDP
Glicogeno (n residui)
H+
Glicogeno (n + 1 residui)

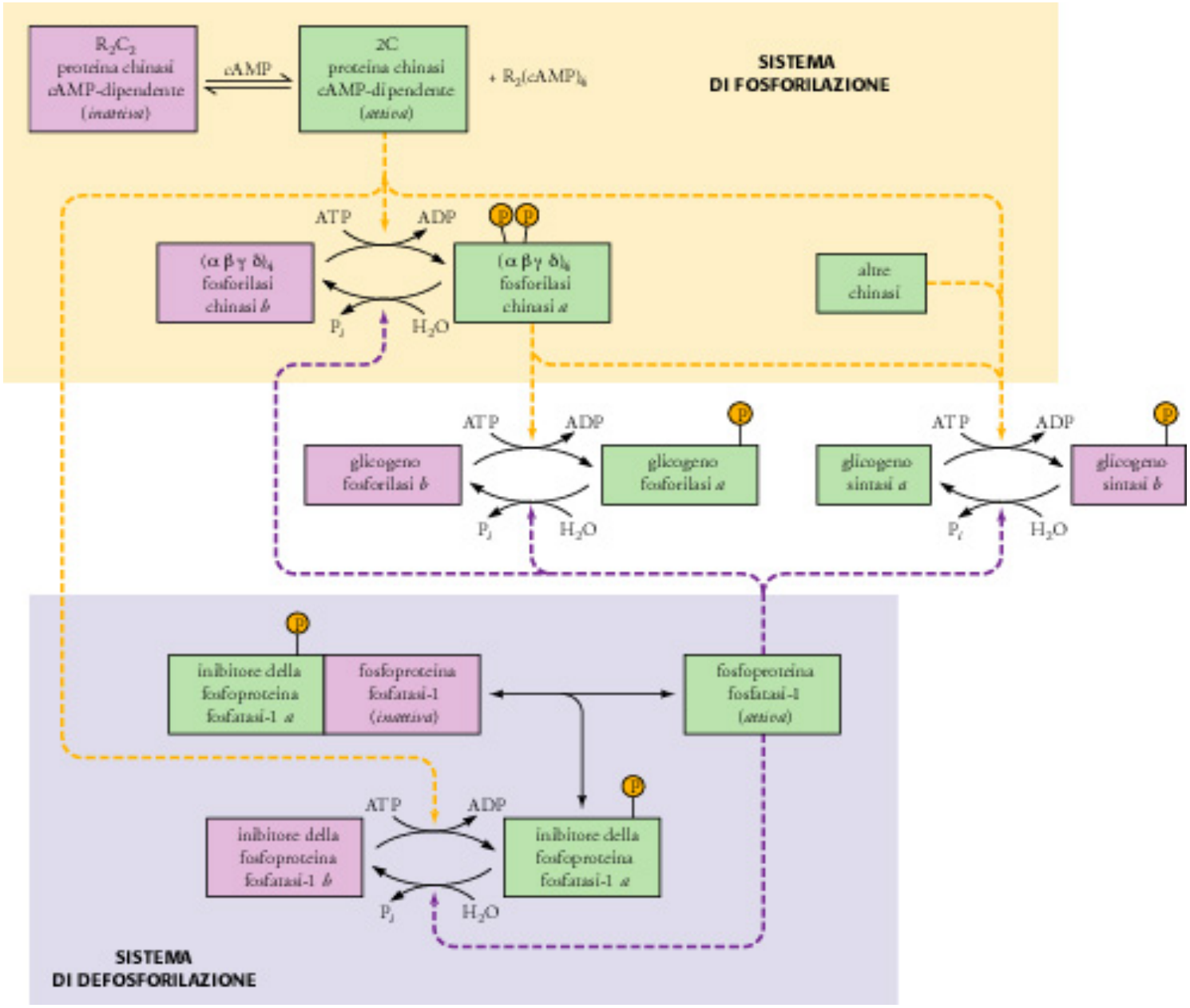

catena terminale
del glicogeno
con legami α(1 → 4)
enzima ramificante

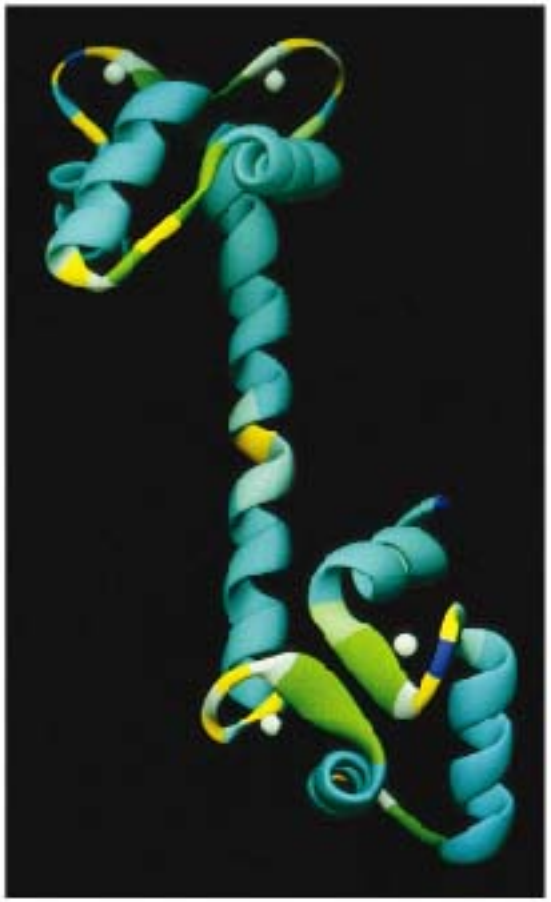

Adenilato ciclasi
Proteina G
Recettore
Membrana cellulare
ATP
cAMP + PPi
C C
R R
Proteina chinasi inattiva
C C + R R cAMP
Proteina chinasi attiva
ATP
OH
O P + ADP
Fosforilasi inattiva b chinasi
Fosforilasi attiva b chinasi
Pi
H2O
2
ATP
Ca2+
HO OH
Fosforilasi b
P O O P
Fosforilasi a
Pi
H2O
Pi
Glicogeno
Glucosio-1 P

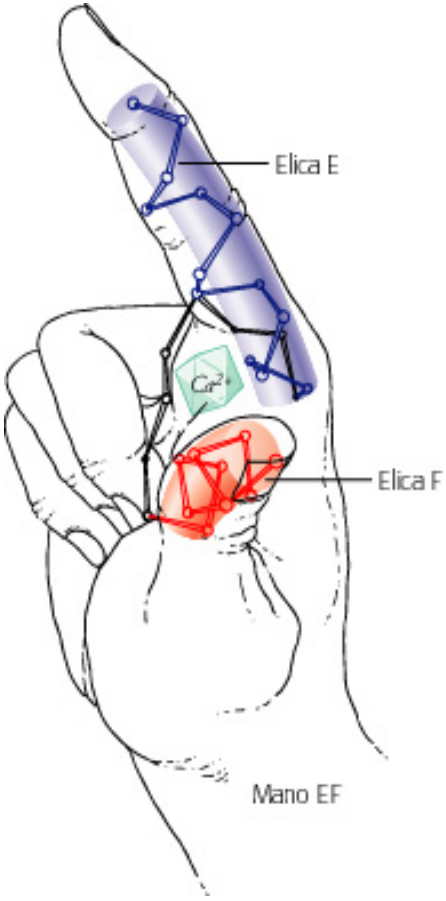

Epinephrine
x molecules
Epinephrine-receptor complex
x molecules
Hepatocyte
$G_{s\alpha}$
ATP
adenylyl cyclase
Cyclic AMP
40x molecules
Inactive PKA
Active PKA
10x molecules
Inactive phosphorylase b kinase
Active phosphorylase b kinase
100x molecules
Inactive glycogen phosphorylase b
Active glycogen phosphorylase a
1,000x molecules
Glycogen
Glucose 1-phosphate
10,000x molecules
Glucose
Blood glucose
10,000x molecules

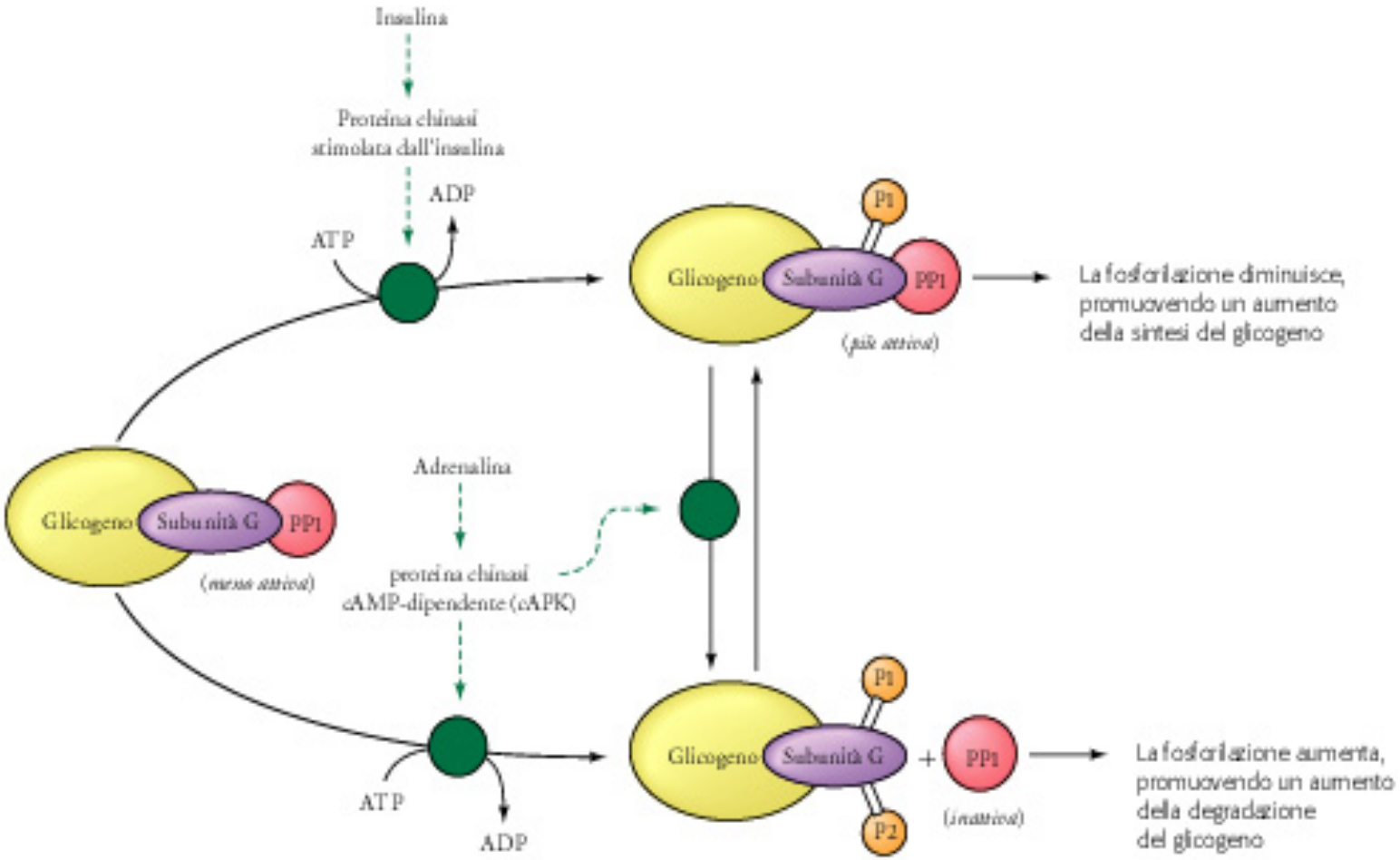

proteina chinasi
cAMP-dipendente
ATP
ADP
P
fosforilasi
chinasi
(meno attiva)
fosforilasi
chinasi
(più attiva)
ATP
ADP
P_i
H_2O
P
glicogeno
fosforilasi b
(meno attiva)
glicogeno
fosforilasi a
(più attiva)
P_i
H_2O
fosfoproteina
fosfatasi-1

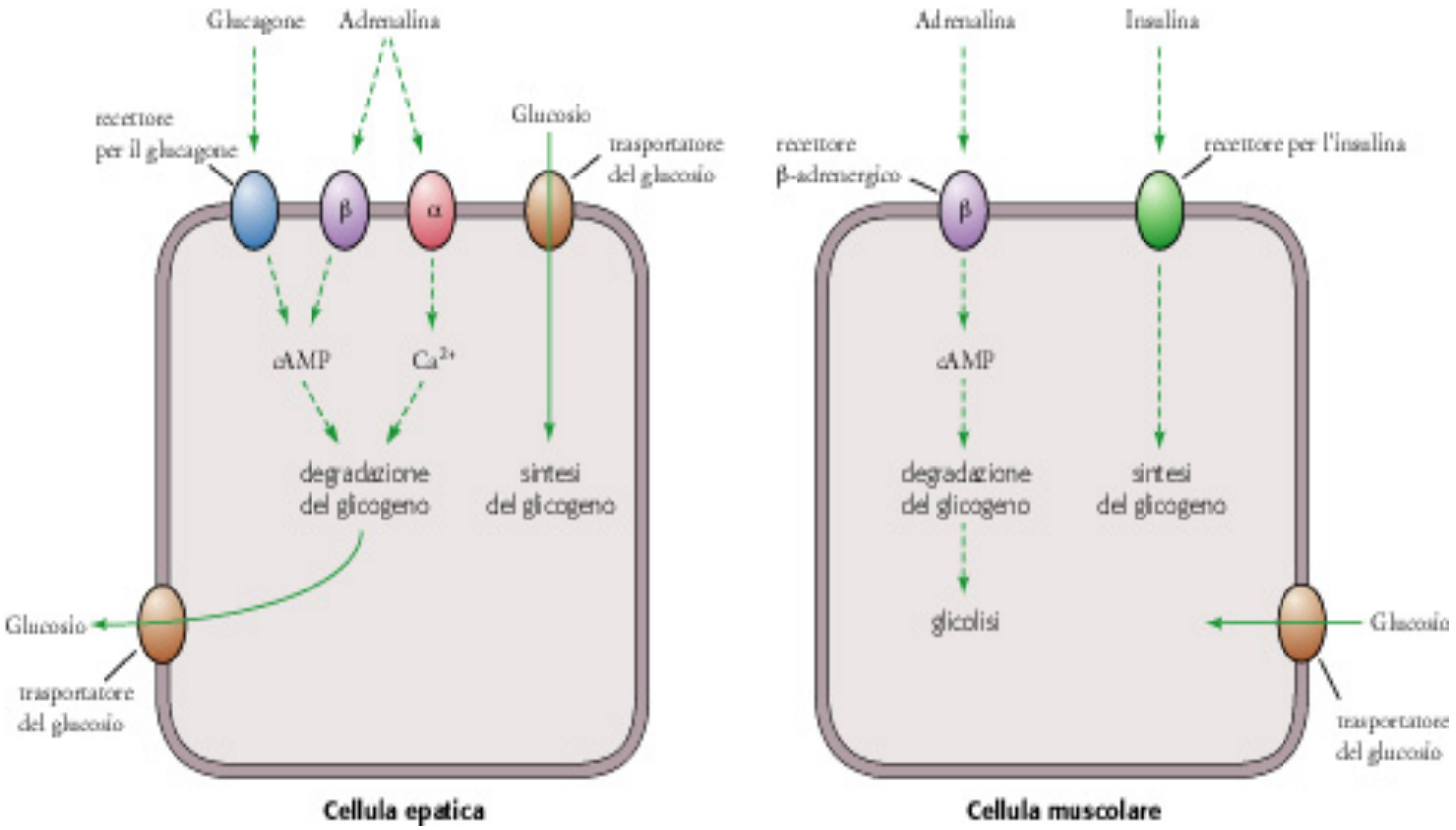

2ATP
2ADP
fosforilasi
chinasi
forma T
(inattiva)
fosfoproteina
fosfatasi
$2P_i$
$2H_2O$
ATP
e/o
G6P
AMP
Glucosio
forma R
(attiva)
Fosforilasi b
Fosforilasi a

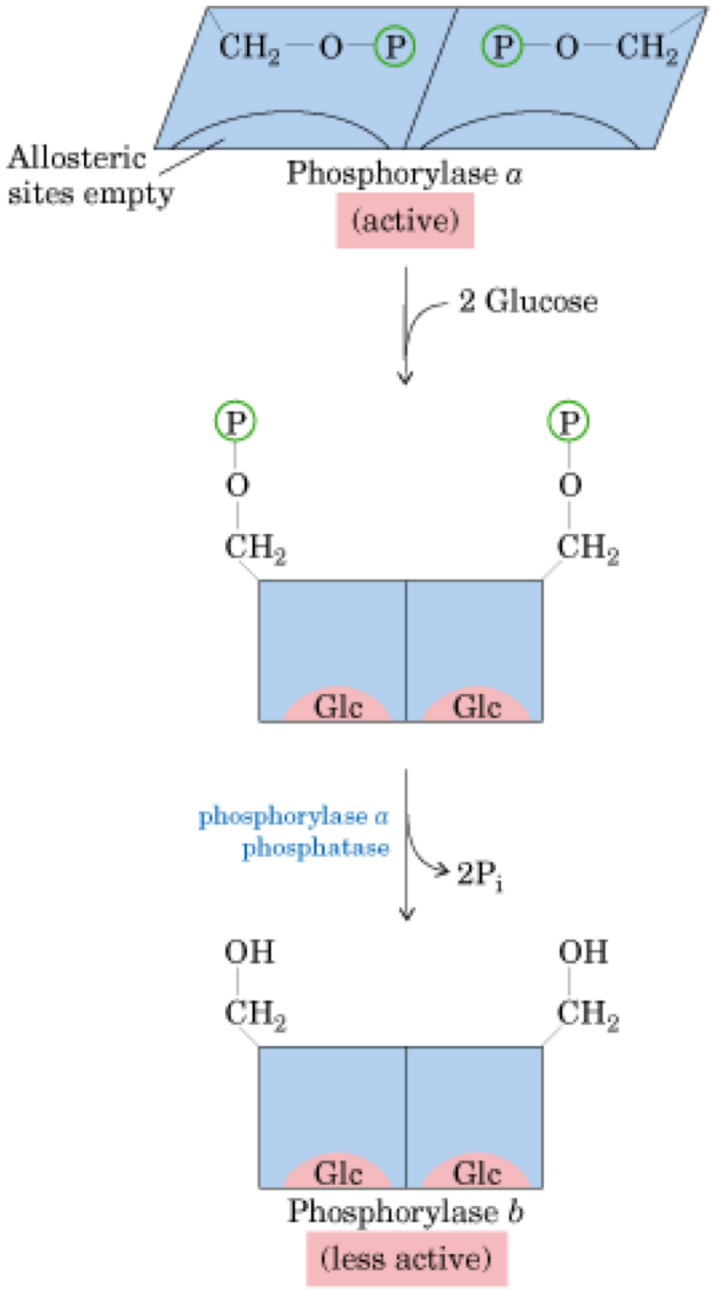

R_2C_2
proteina chinasi cAMP-dipendente (*inattiva*)
cAMP
2C
proteina chinasi cAMP-dipendente (*attiva*)
+ $R_2(cAMP)_4$
SISTEMA DI FOSFORILAZIONE
ATP
ADP
$(\alpha\beta\gamma\delta)_4$ fosforilasi chinasi *b*
$(\alpha\beta\gamma\delta)_4$ fosforilasi chinasi *a*
altre chinasi
P_i
H_2O
glicogeno fosforilasi *b*
glicogeno fosforilasi *a*
glicogeno sintasi *a*
glicogeno sintasi *b*
inibitore della fosfoproteina fosfatasi-1 *a*
fosfoproteina fosfatasi-1 (*inattiva*)
fosfoproteina fosfatasi-1 (*attiva*)
inibitore della fosfoproteina fosfatasi-1 *b*
inibitore della fosfoproteina fosfatasi-1 *a*
SISTEMA DI DEFOSFORILAZIONE

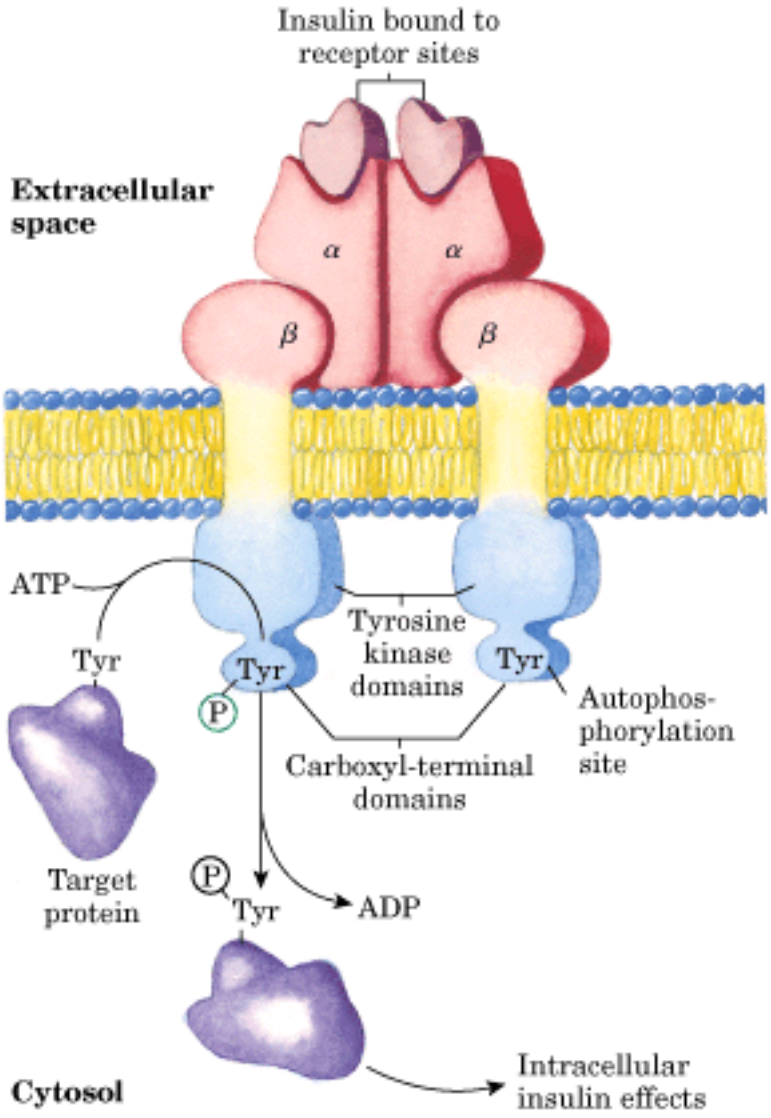


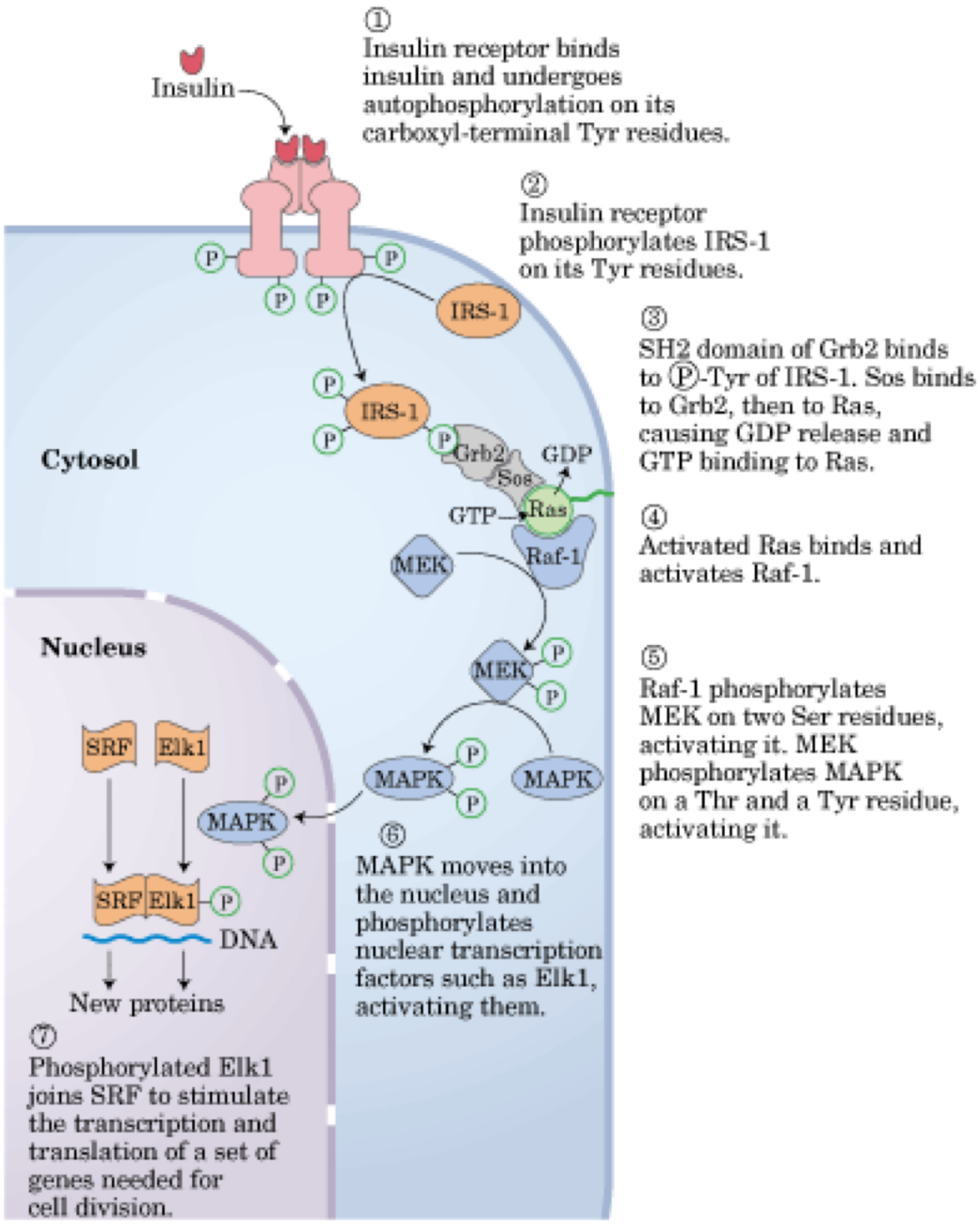

Elica E
Ca2+
Elica F
Mano EF

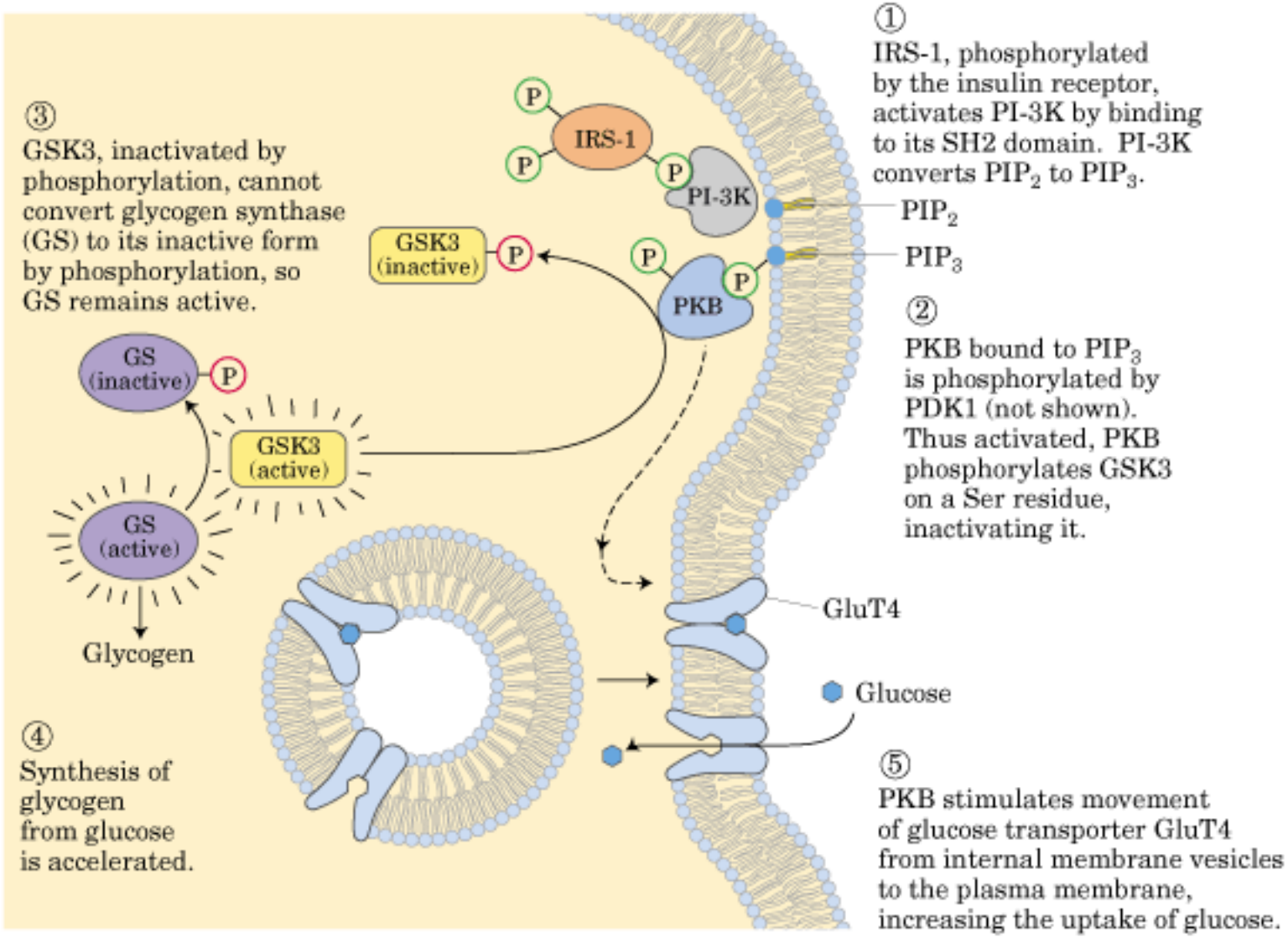

Insulina
Proteina chinasi stimolata dall'insulina
ADP
ATP
Glicogeno
Subunità G
PP1
(più attiva)
La fosforilazione diminuisce, promuovendo un aumento della sintesi del glicogeno
Glicogeno
Subunità G
PP1
(meno attiva)
Adrenalina
proteina chinasi cAMP-dipendente (cAPK)
ATP
ADP
Glicogeno
Subunità G
P1
P2
PP1
(inattiva)
La fosforilazione aumenta, promuovendo un aumento della degradazione del glicogeno

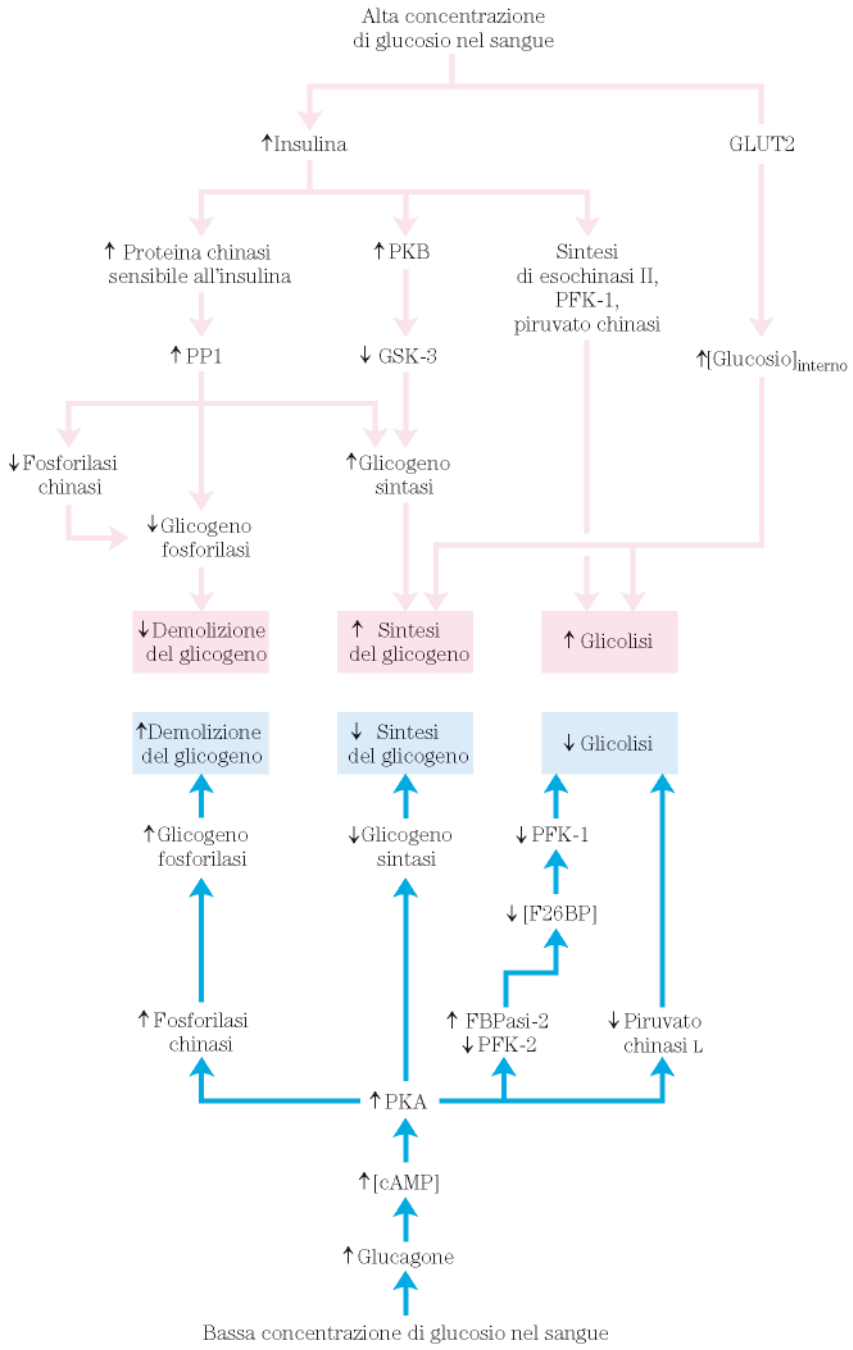

Glucagone
Adrenalina
recettore per il glucagone
β
α
Glucosio
trasportatore del glucosio
cAMP
Ca^{2+}
degradazione del glicogeno
sintesi del glicogeno
Glucosio
trasportatore del glucosio
Cellula epatica
Adrenalina
Insulina
recettore β-adrenergico
β
recettore per l'insulina
cAMP
degradazione del glicogeno
sintesi del glicogeno
glicolisi
Glucosio
trasportatore del glucosio
Cellula muscolare


CH2 — O — P
P — O — CH2
Allosteric sites empty
Phosphorylase a
(active)
2 Glucose
P
O
CH2
Glc
Glc
phosphorylase a phosphatase
2Pi
OH
CH2
Glc
Glc
Phosphorylase b
(less active)


Insulin bound to receptor sites
Extracellular space
α
α
β
β
ATP
Tyr
Tyr
P
Tyrosine kinase domains
Tyr
Autophos-phorylation site
Carboxyl-terminal domains
Target protein
P
Tyr
ADP
Cytosol
Intracellular insulin effects


① Insulin receptor binds insulin and undergoes autophosphorylation on its carboxyl-terminal Tyr residues.
Insulin
② Insulin receptor phosphorylates IRS-1 on its Tyr residues.
IRS-1
③ SH2 domain of Grb2 binds to Ⓟ-Tyr of IRS-1. Sos binds to Grb2, then to Ras, causing GDP release and GTP binding to Ras.
Grb2
Sos
GDP
GTP
Ras
④ Activated Ras binds and activates Raf-1.
MEK
Raf-1
⑤ Raf-1 phosphorylates MEK on two Ser residues, activating it. MEK phosphorylates MAPK on a Thr and a Tyr residue, activating it.
MAPK
⑥ MAPK moves into the nucleus and phosphorylates nuclear transcription factors such as Elk1, activating them.
Cytosol
Nucleus
SRF
Elk1
DNA
New proteins
⑦ Phosphorylated Elk1 joins SRF to stimulate the transcription and translation of a set of genes needed for cell division.


①
IRS-1, phosphorylated by the insulin receptor, activates PI-3K by binding to its SH2 domain. PI-3K converts PIP_2 to PIP_3.
PIP_2
PIP_3
②
PKB bound to PIP_3 is phosphorylated by PDK1 (not shown). Thus activated, PKB phosphorylates GSK3 on a Ser residue, inactivating it.
③
GSK3, inactivated by phosphorylation, cannot convert glycogen synthase (GS) to its inactive form by phosphorylation, so GS remains active.
④
Synthesis of glycogen from glucose is accelerated.
⑤
PKB stimulates movement of glucose transporter GluT4 from internal membrane vesicles to the plasma membrane, increasing the uptake of glucose.
P
IRS-1
PI-3K
PKB
GSK3 (inactive)
GSK3 (active)
GS (inactive)
GS (active)
Glycogen
GluT4
Glucose


Alta concentrazione di glucosio nel sangue
↑Insulina
GLUT2
↑ Proteina chinasi sensibile all'insulina
↑PKB
Sintesi di esochinasi II, PFK-1, piruvato chinasi
↑PP1
↓ GSK-3
↑[Glucosio]interno
↓Fosforilasi chinasi
↑Glicogeno sintasi
↓Glicogeno fosforilasi
↓Demolizione del glicogeno
↑ Sintesi del glicogeno
↑ Glicolisi
↑Demolizione del glicogeno
↓ Sintesi del glicogeno
↓ Glicolisi
↑Glicogeno fosforilasi
↓Glicogeno sintasi
↓ PFK-1
↓ [F26BP]
↑ Fosforilasi chinasi
↑ FBPasi-2 ↓ PFK-2
↓ Piruvato chinasi L
↑PKA
↑[cAMP]
↑Glucagone
Bassa concentrazione di glucosio nel sangue