G –Protein Coupled Receptor

By

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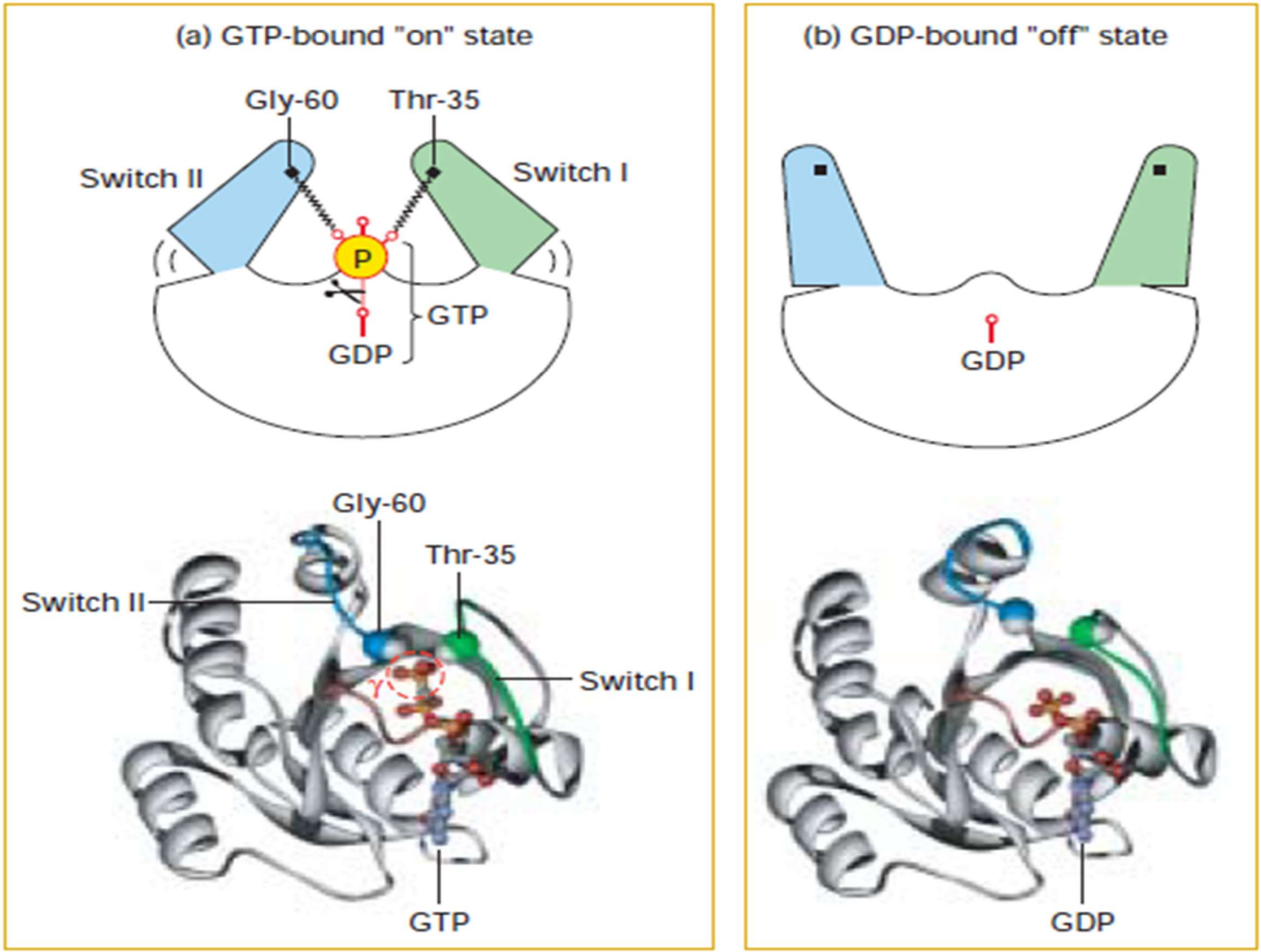

(a) GTP-bound "on" state
Gly-60
Thr-35
Switch II
Switch I
P
GTP
GDP
(b) GDP-bound "off" state
GDP
Gly-60
Thr-35
Switch II
Switch I
γ
GTP
GDP

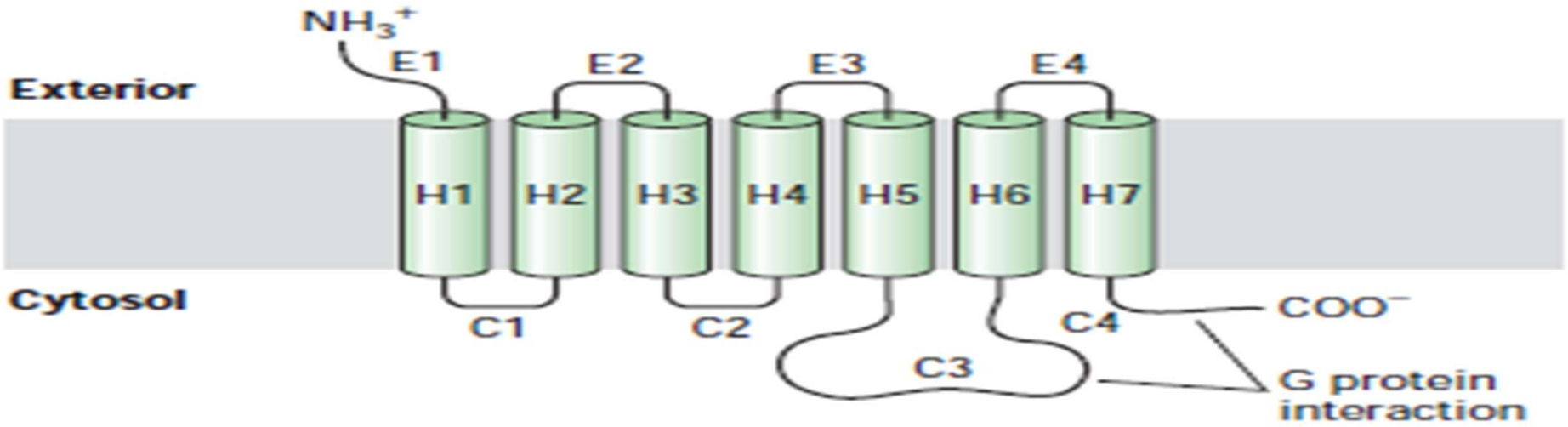
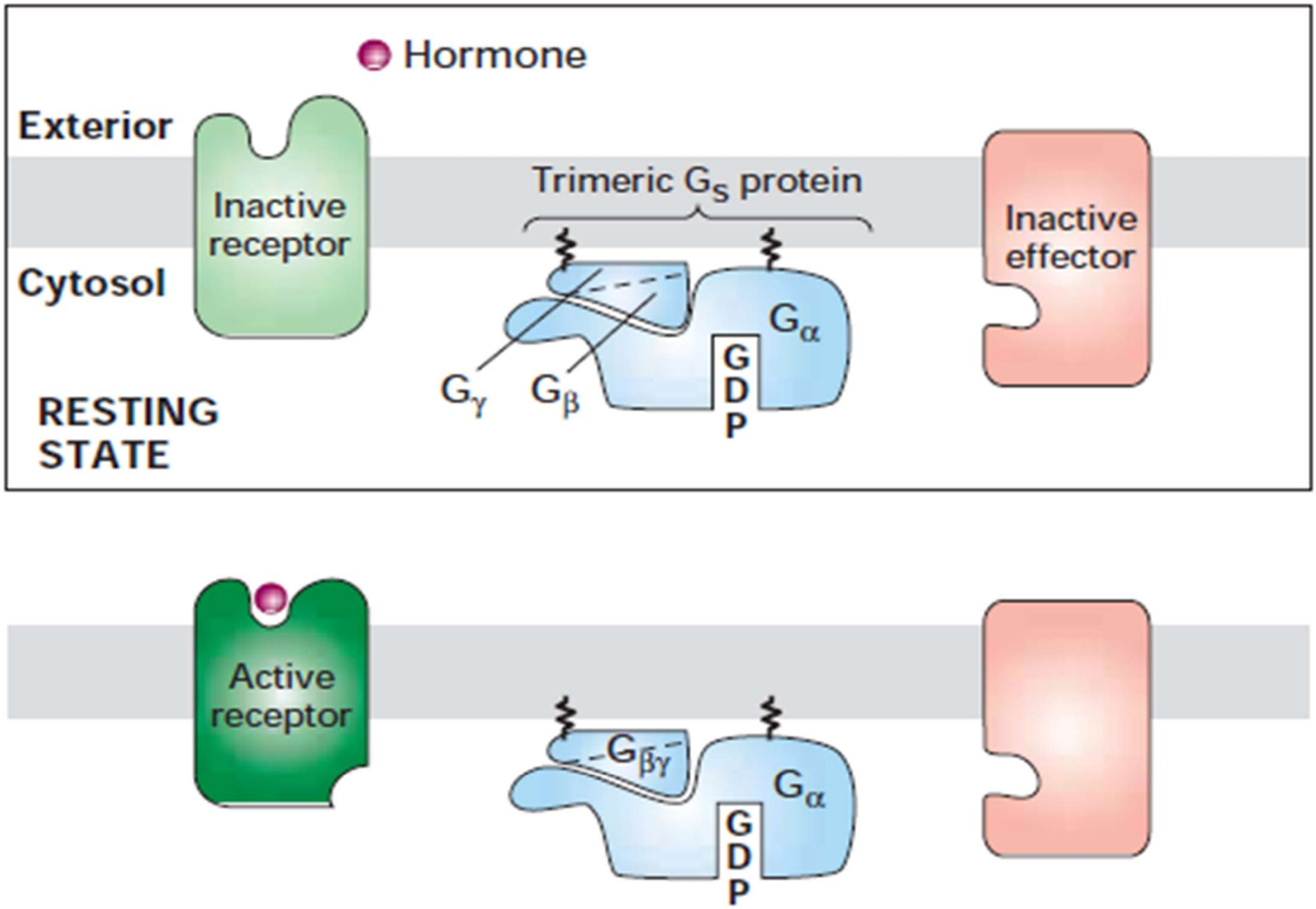

NH_3^+
E1
E2
E3
E4
Exterior
H1
H2
H3
H4
H5
H6
H7
Cytosol
C1
C2
C3
C4
COO^-
G protein interaction

TABLE 13-1 Major Classes of Mammalian Trimeric G Proteins and Their Effectors*

G_α Class	Associated Effector	2nd Messenger	Receptor Examples
$G_{s\alpha}$	Adenylyl cyclase	cAMP (increased)	β-Adrenergic (epinephrine) receptor; receptors for glucagon, serotonin, vasopressin
$G_{i\alpha}$	Adenylyl cyclase K^+ channel ($G_{\beta\gamma}$ activates effector)	cAMP (decreased) Change in membrane potential	α_1-Adrenergic receptor Muscarinic acetylcholine receptor
$G_{olf\alpha}$	Adenylyl cyclase	cAMP (increased)	Odorant receptors in nose
$G_{q\alpha}$	Phospholipase C	IP_3, DAG (increased)	α_2-Adrenergic receptor
$G_{o\alpha}$	Phospholipase C	IP_3, DAG (increased)	Acetylcholine receptor in endothelial cells
$G_{t\alpha}$	cGMP phosphodiesterase	cGMP (decreased)	Rhodopsin (light receptor) rod cells

*A given G_α subclass may be associated with more than one effector protein. To date, only one major $G_{s\alpha}$ has been identified, but multiple $G_{q\alpha}$ an $G_{i\alpha}$ proteins have been described. Effector proteins commonly are regulated by G_α but in some cases by $G_{\beta\gamma}$ or the combined action of G_α and G_β. IP_3 = inositol 1,4,5-trisphosphate; DAG = 1,2-diacylglycerol.

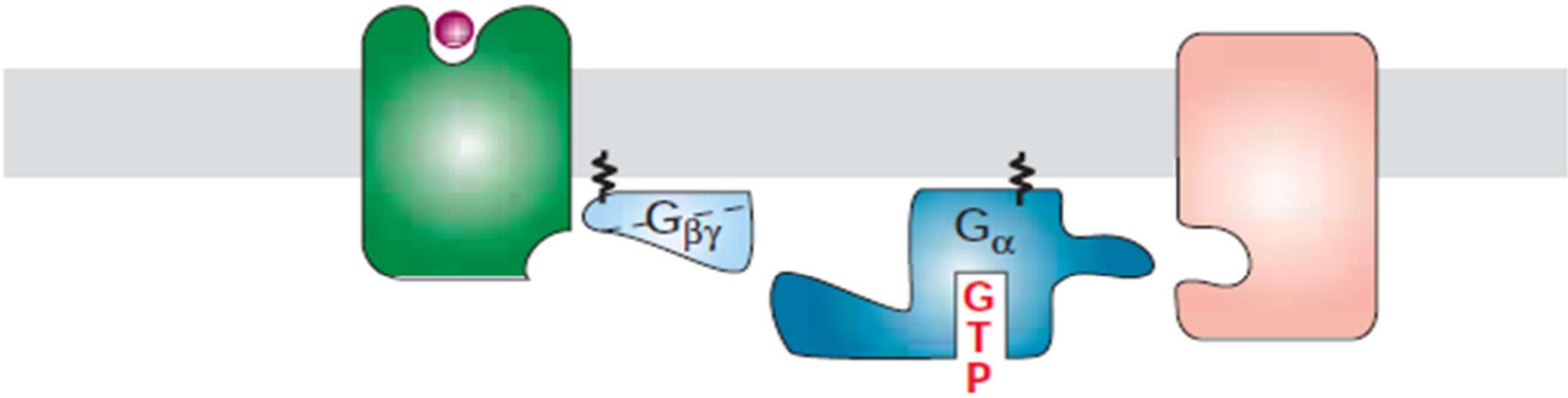
SOURCES: See L. Birnbaumer, 1992, *Cell* **71**:1069; Z. Farfel et al., 1999, *New Eng. J. Med.* **340**:1012; and K. Pierce et al., 2002, *Nature Rev. Mol. Cell Biol.* **3**:639.



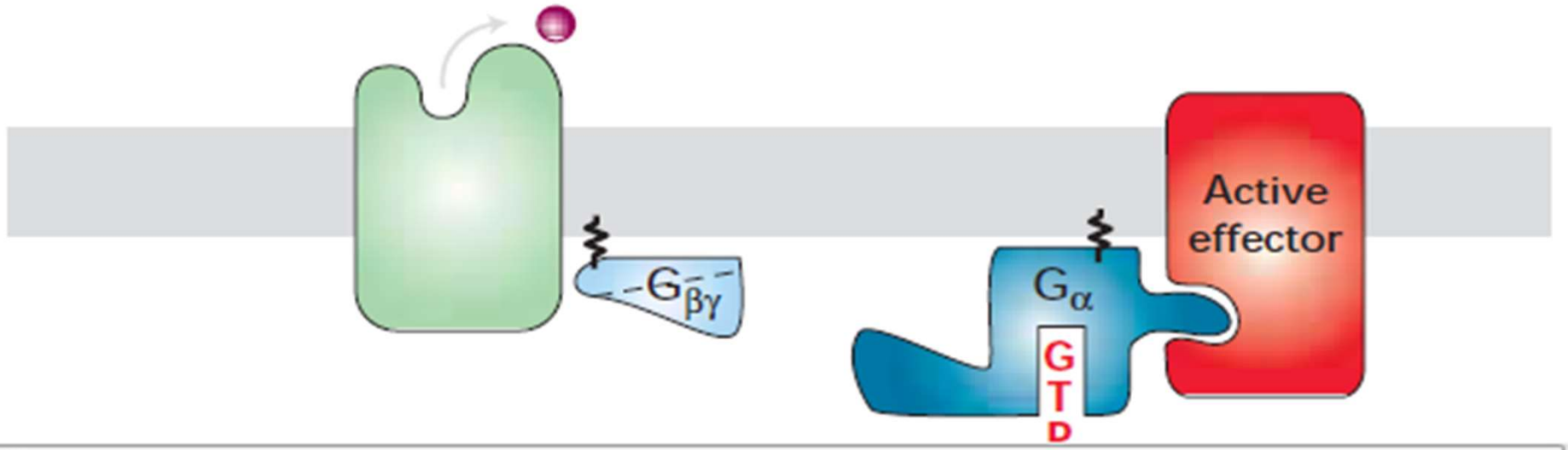
1 Binding of hormone induces a conformational change in receptor

P

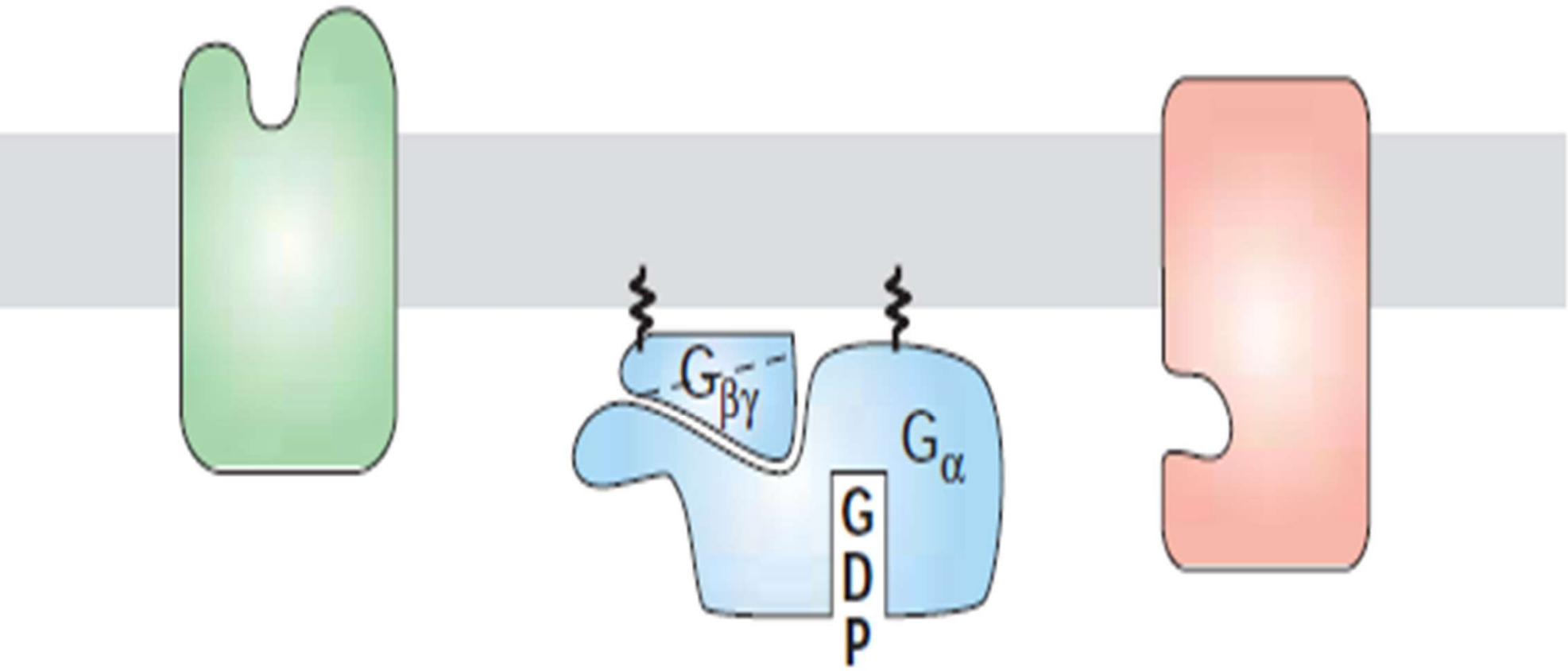
2 Activated receptor binds to G_α subunit



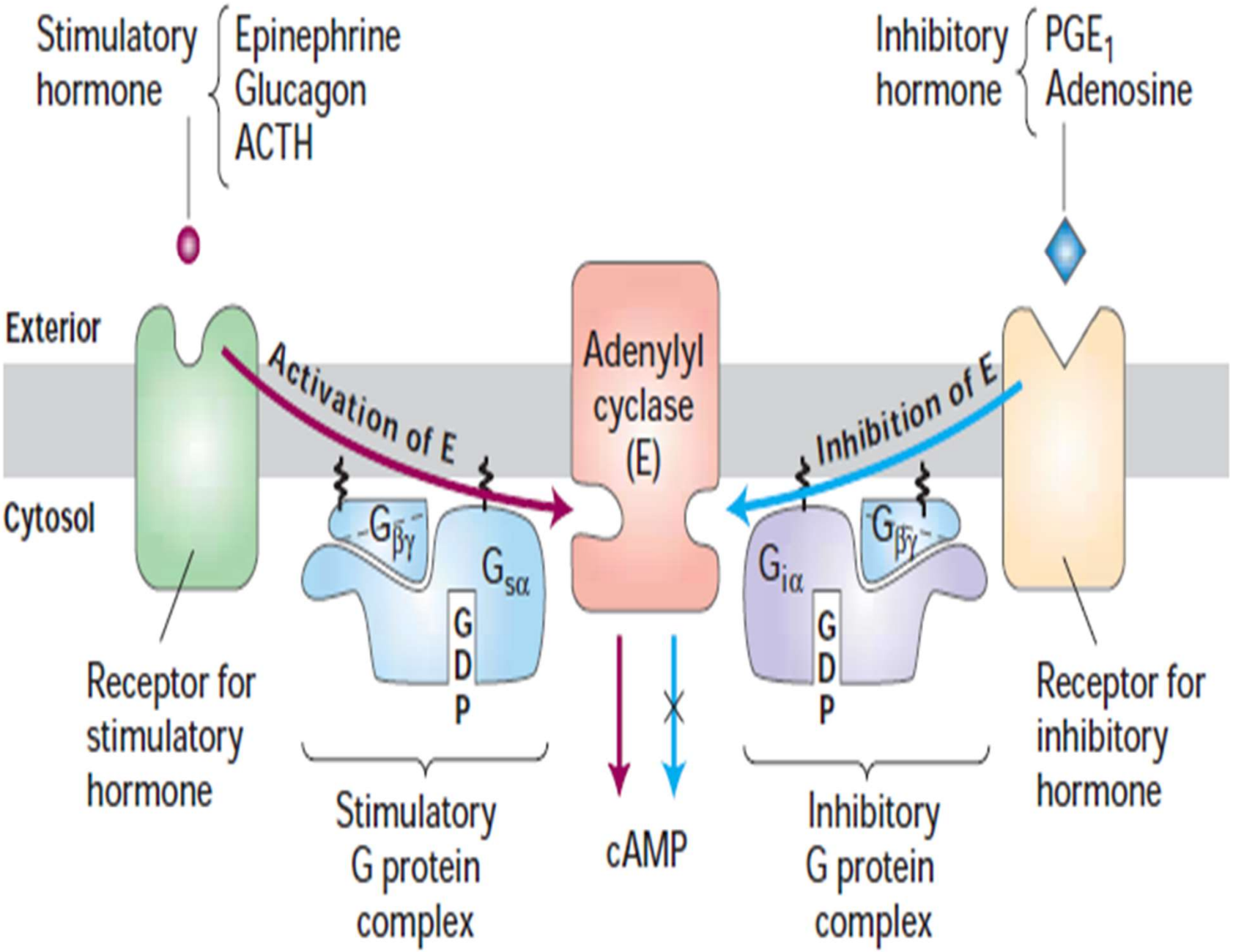
3 Binding induces conformational change in G_α; bound GDP dissociates and is replaced by GTP; G_α dissociates from $G_{\beta\gamma}$

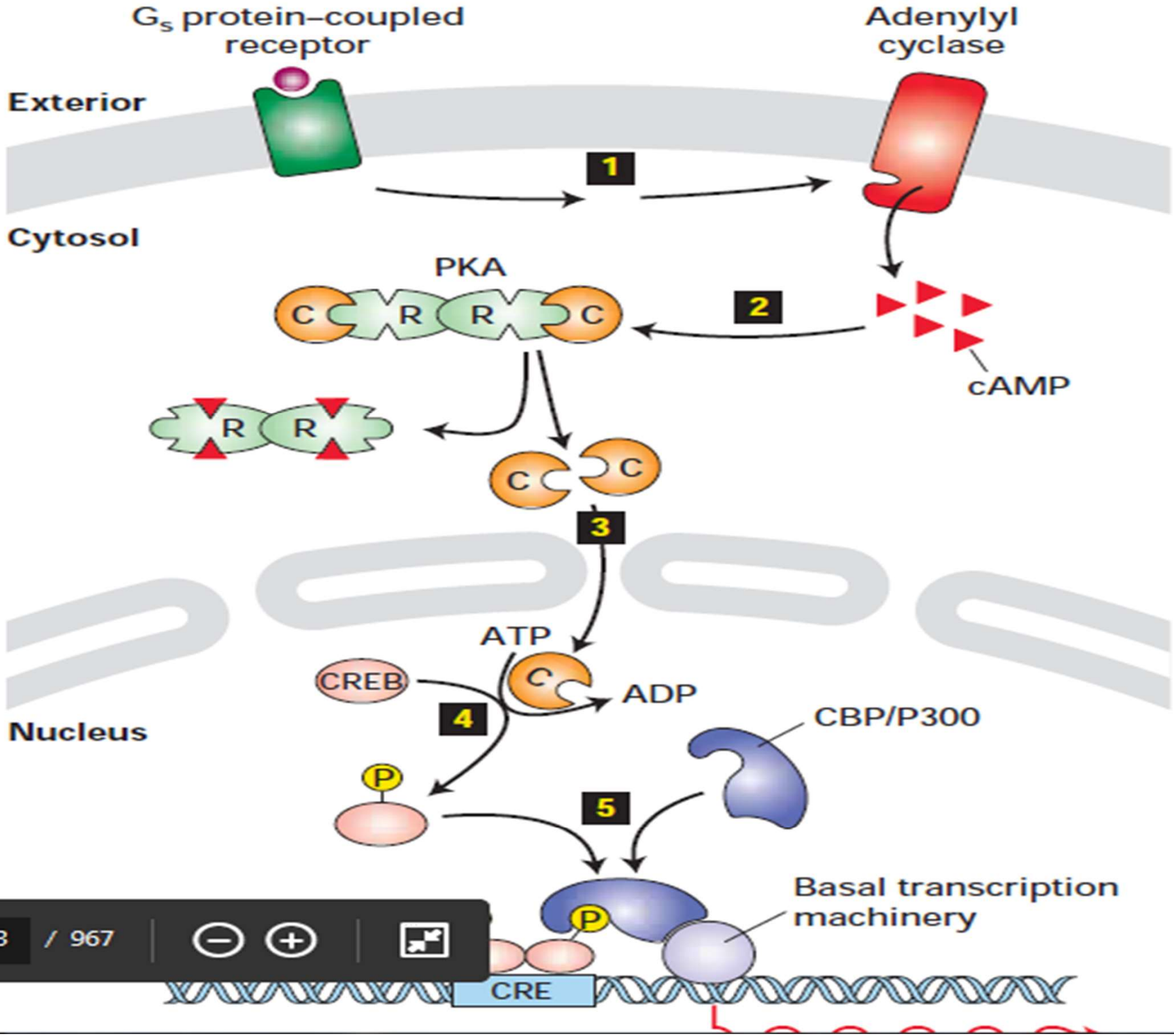


4 Hormone dissociates from receptor, G_α binds to effector, activating it



5 Hydrolysis of GTP to GDP causes G_α to dissociate from effector and reassociate with $G_{\beta\gamma}$


Stimulatory hormone
Epinephrine
Glucagon
ACTH
Inhibitory hormone
PGE1
Adenosine
Exterior
Cytosol
Activation of E
Inhibition of E
Adenylyl cyclase (E)
Gβγ
Gsα
Giα
G
D
P
Receptor for stimulatory hormone
Receptor for inhibitory hormone
Stimulatory G protein complex
Inhibitory G protein complex
cAMP


G_s protein–coupled receptor
Adenylyl cyclase
Exterior
Cytosol
PKA
C
R
R
C
1
2
cAMP
R
R
C
C
3
ATP
CREB
C
ADP
4
Nucleus
CBP/P300
P
5
P
Basal transcription machinery
CRE

▶ FIGURE 13-32 Activation of gene expression following ligand binding to G_s protein–coupled receptors. Receptor stimulation (1) leads to activation of PKA (2). Catalytic subunits of PKA translocate to the nucleus (3) and there phosphorylate and activate the transcription factor CREB (4). Phosphorylated CREB associates with the co-activator CBP/P300 (5) to stimulate various target genes controlled by the CRE regulatory element. See the text for details. [See K. A. Lee and N. Masson, 1993, *Biochim. Biophys. Acta* **1174**:221, and D. Parker et al., 1996, *Mol. Cell Biol.* **16**(2):694.]

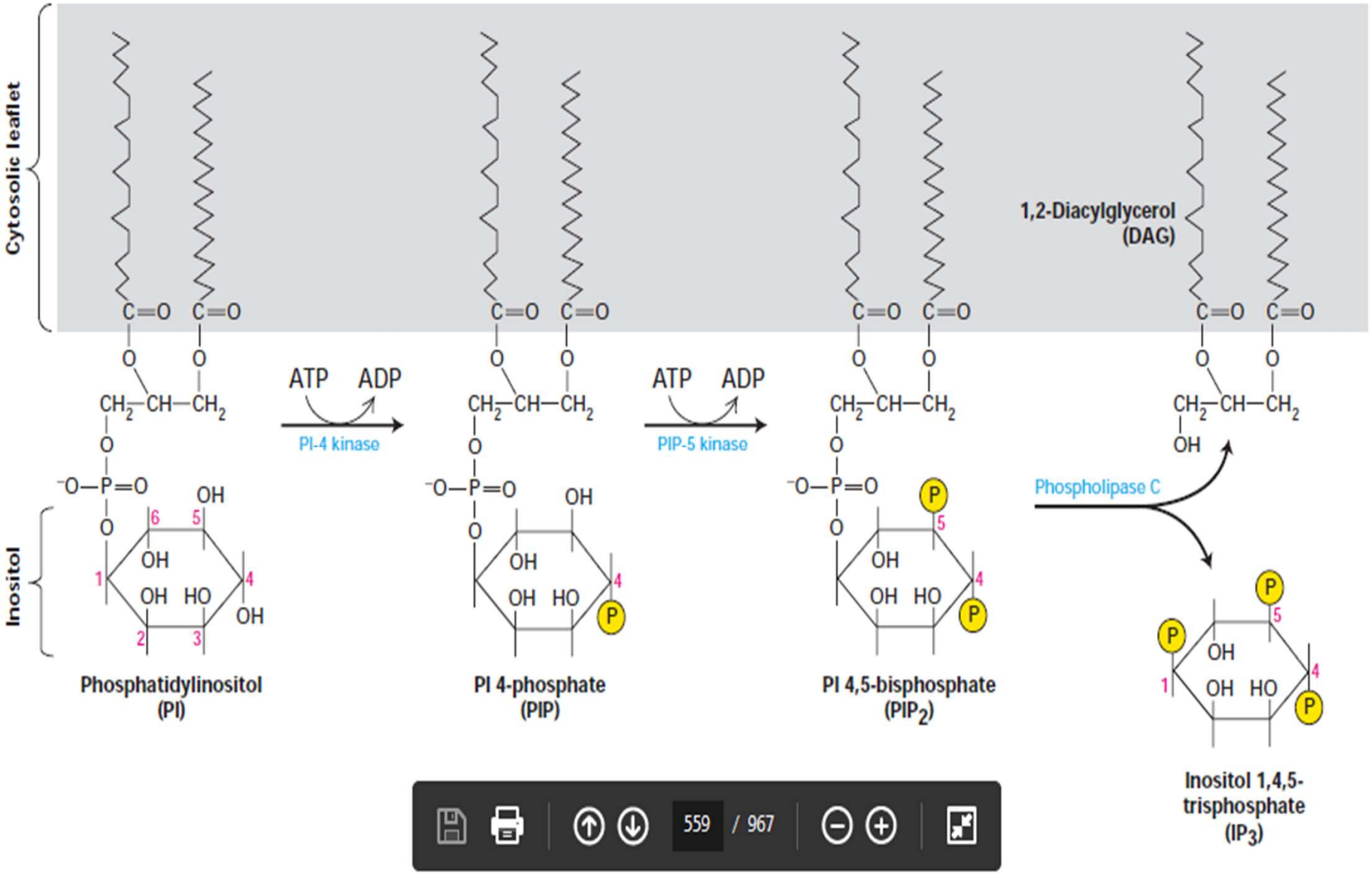
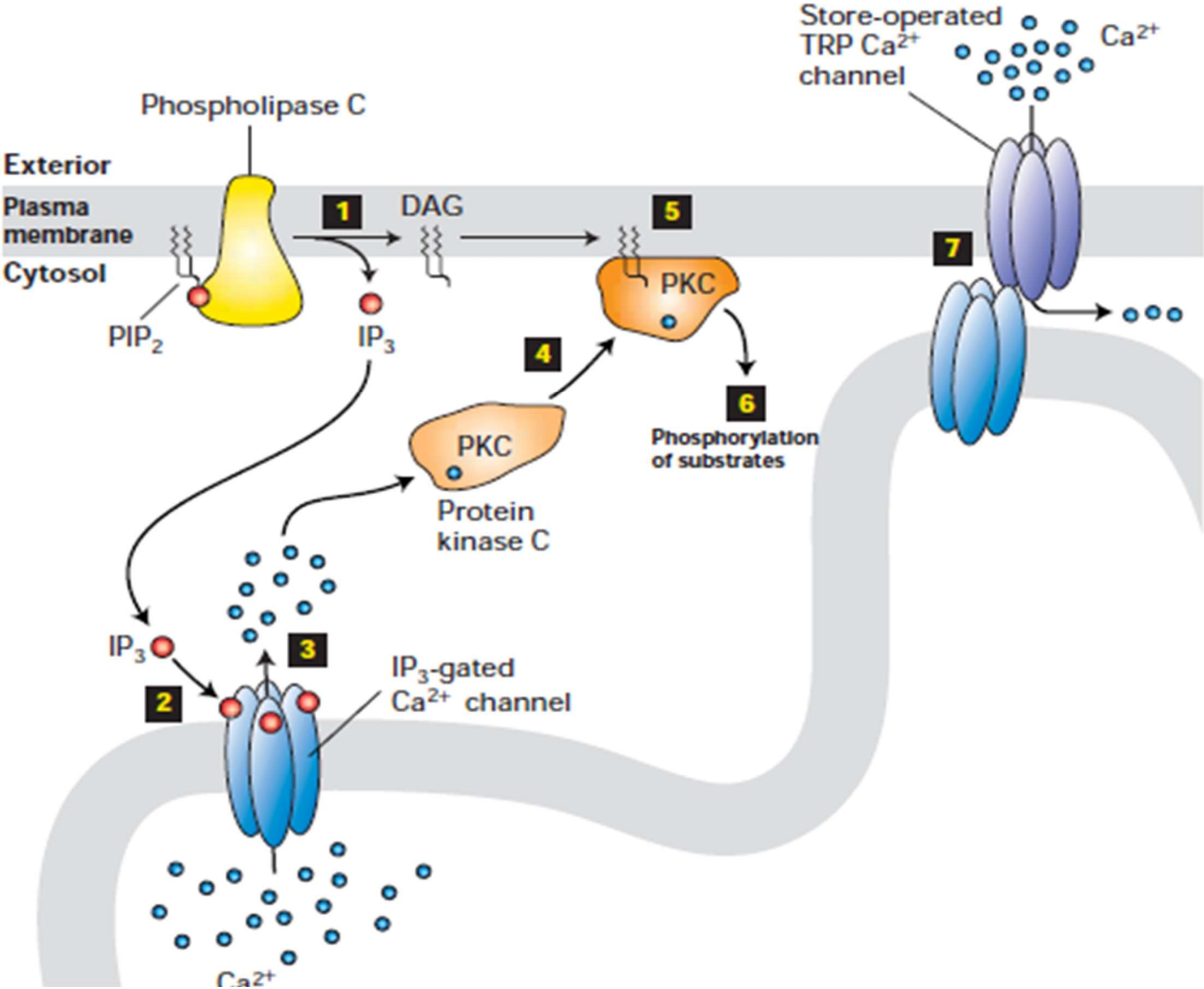
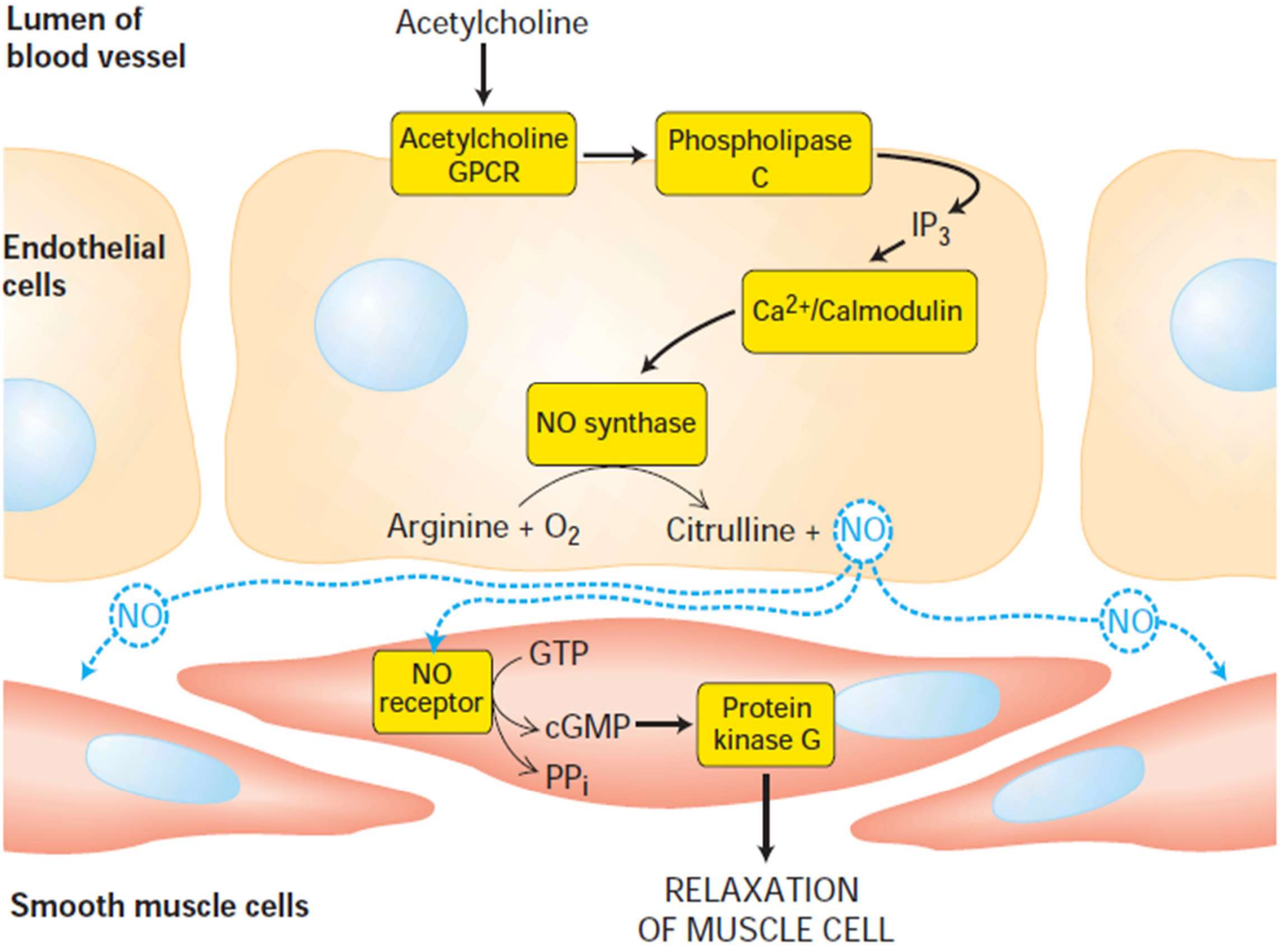
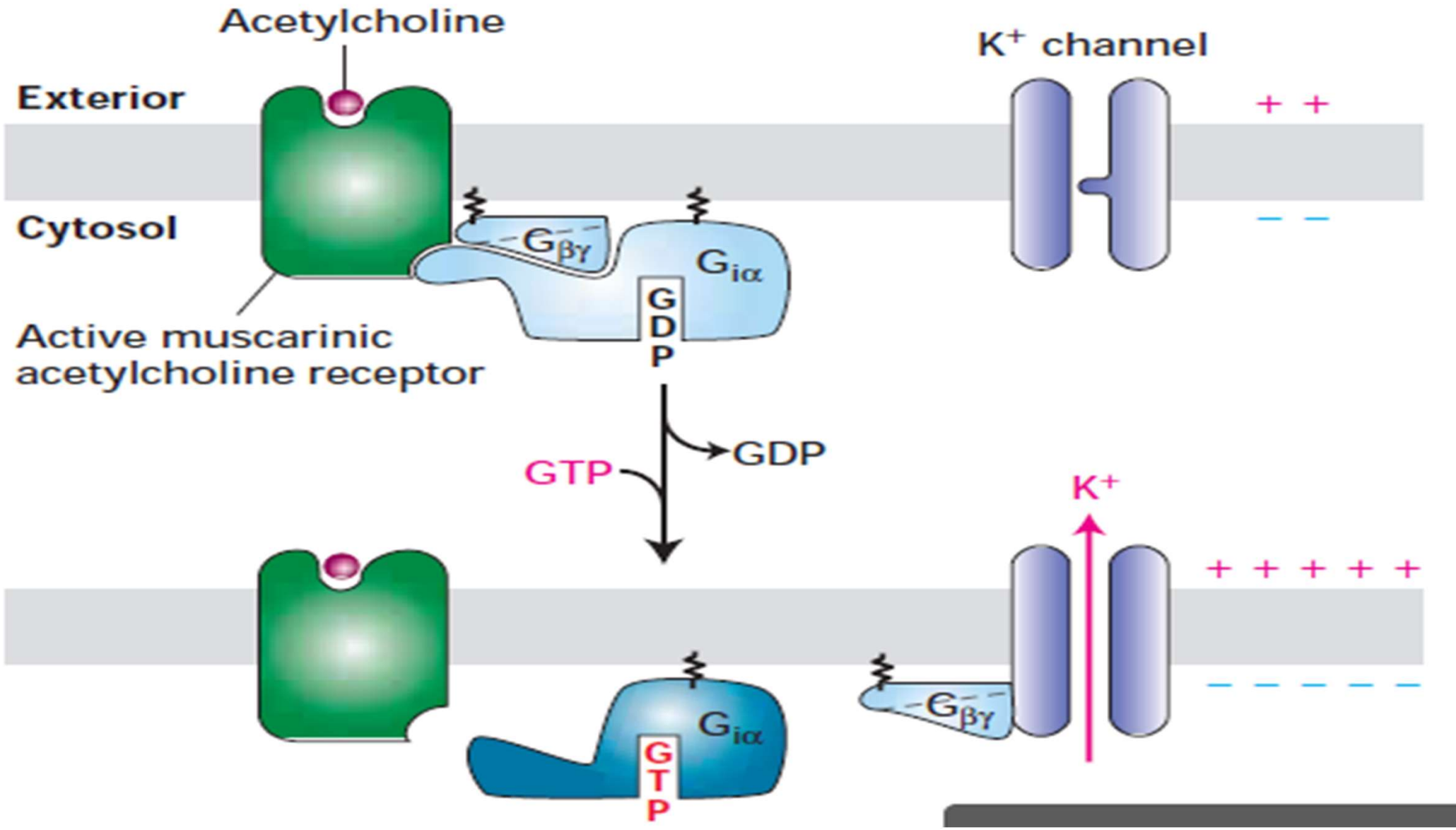


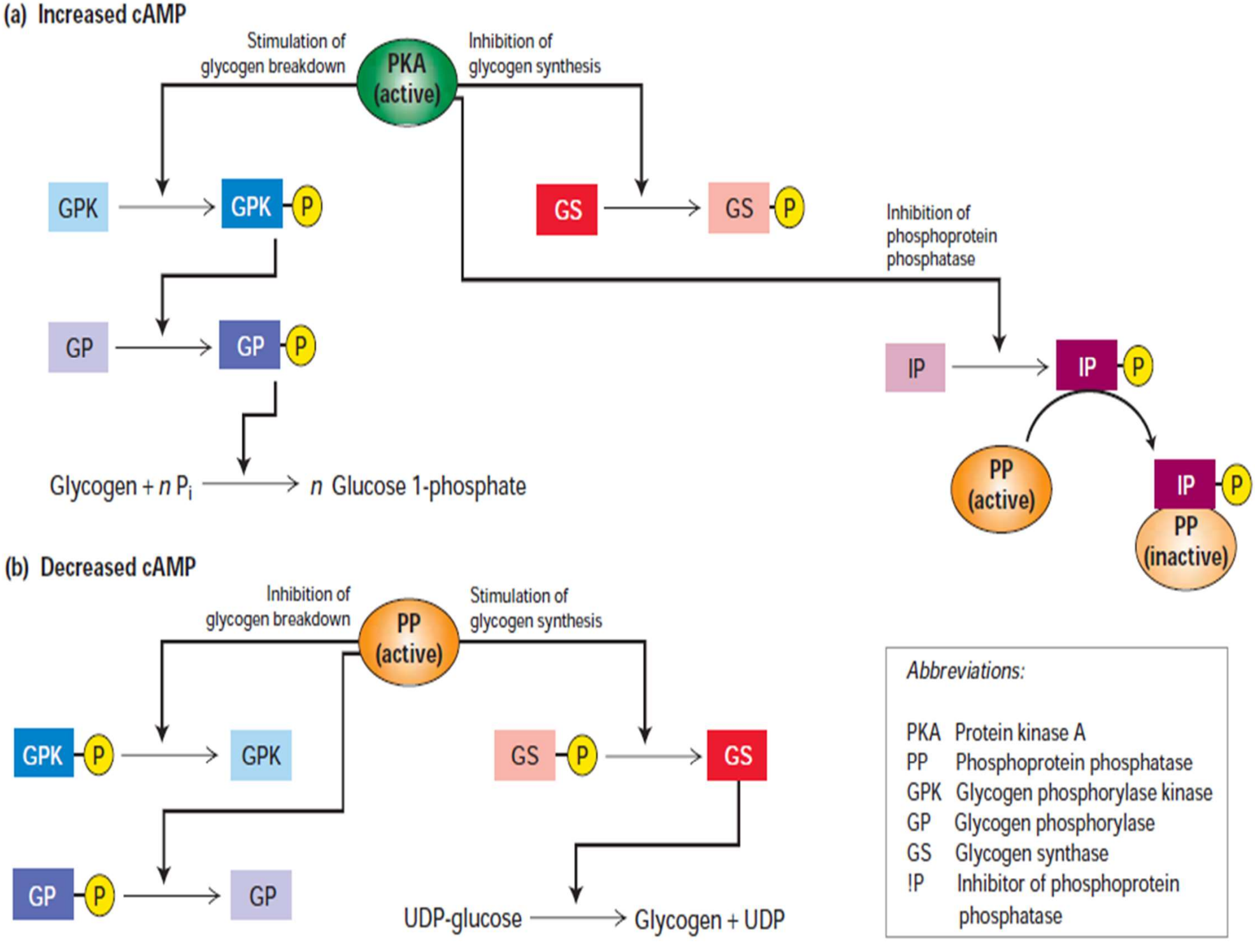
FIGURE 13-28 Synthesis of DAG and IP_3 from PIP and PIP_2. Cleavage of PIP_2 by phospholipase C (PLC) yields

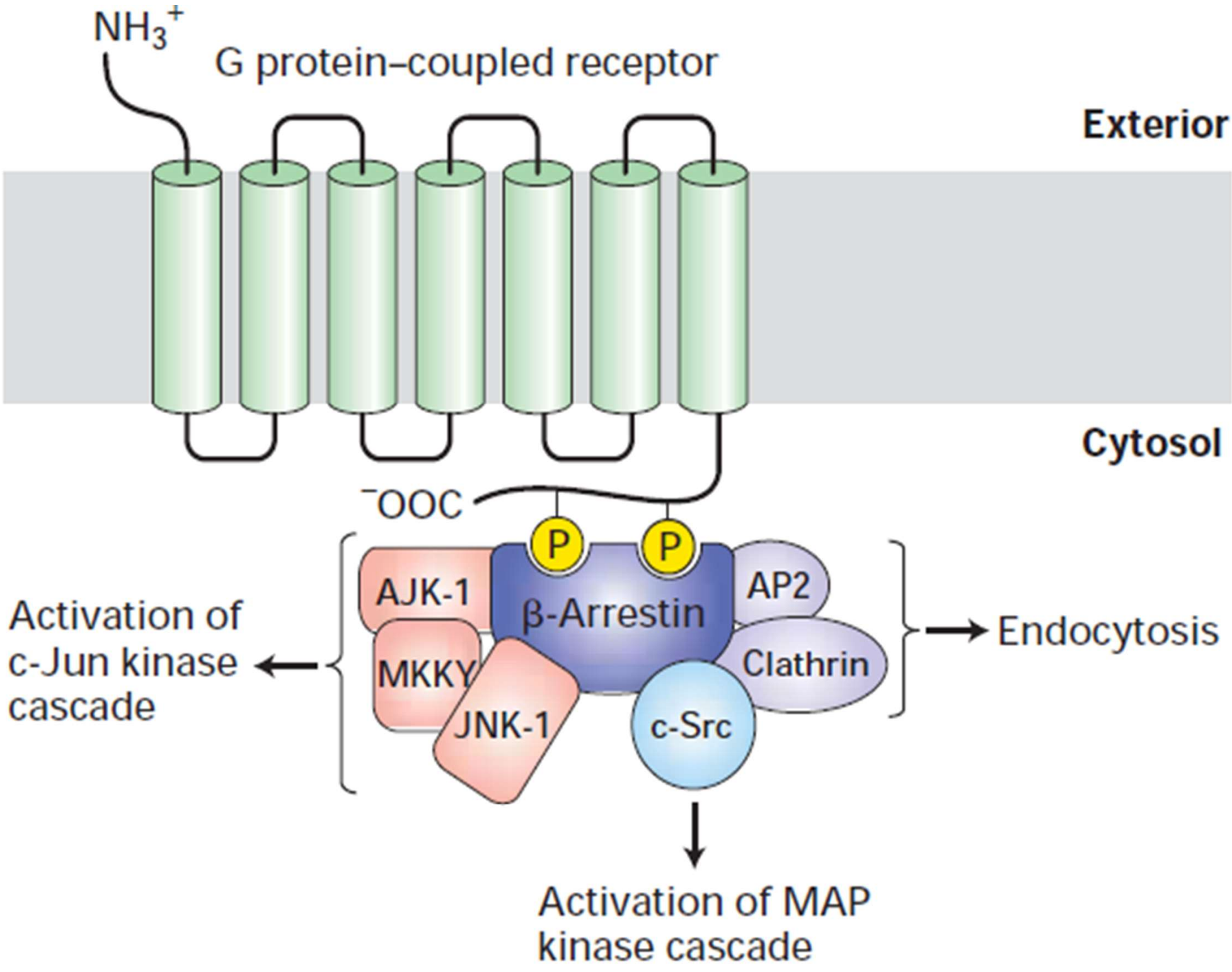

Store-operated
TRP Ca^{2+}
channel
Ca^{2+}
Phospholipase C
Exterior
Plasma
membrane
Cytosol
1
DAG
5
PKC
7
PIP_2
IP_3
4
6
Phosphorylation
of substrates
PKC
Protein
kinase C
IP_3
3
2
IP_3-gated
Ca^{2+} channel
Ca^{2+}

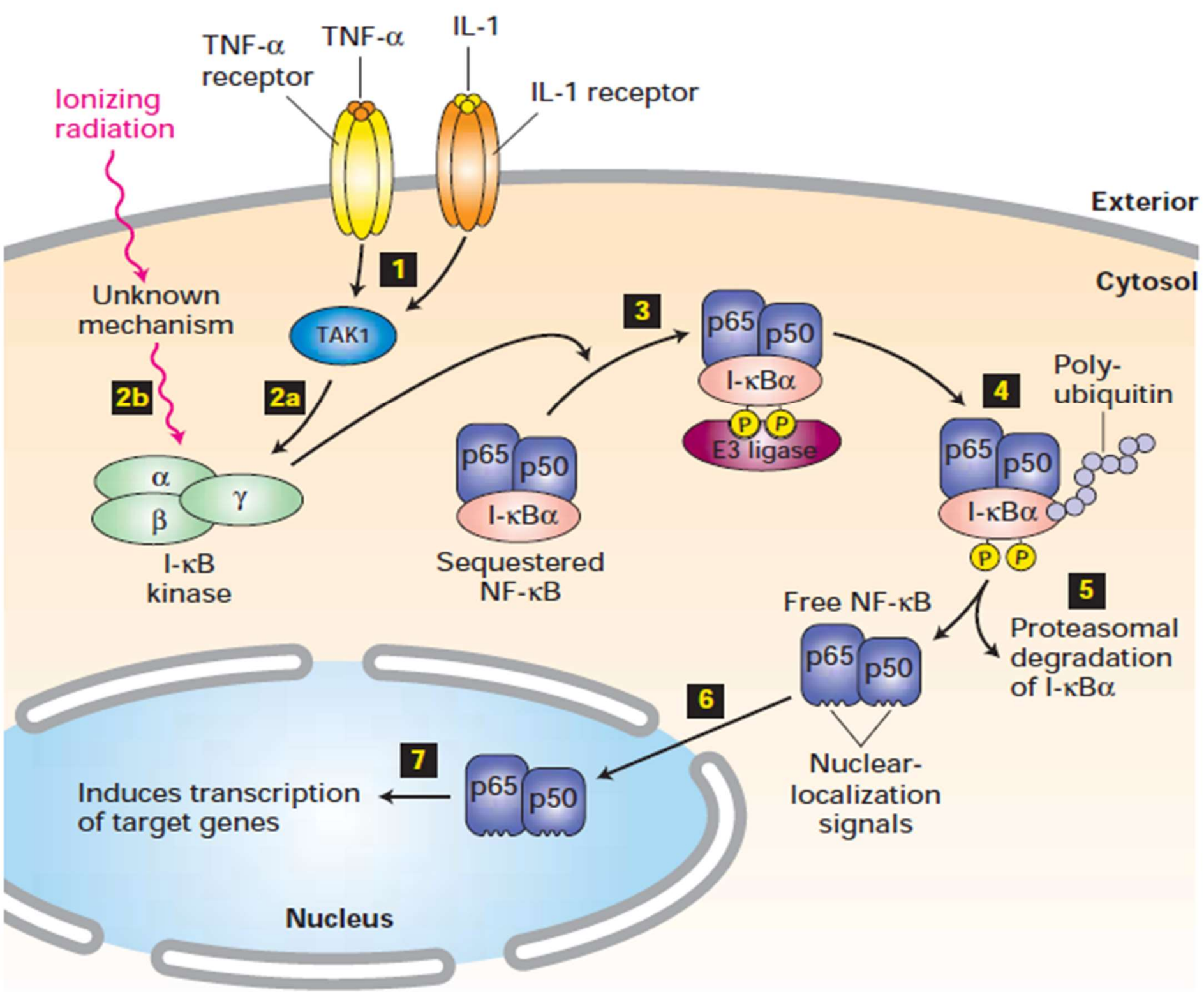
◀ FIGURE 13-29 IP_3/DAG pathway and the elevation of cytosolic Ca^{2+}. This pathway can be triggered by ligand binding to certain G protein–coupled receptors and several other receptor types, leading to activation of phospholipase C. Cleavage of PIP_2 by phospholipase C yields IP_3 and DAG (step 1). After diffusing through the cytosol, IP_3 interacts with and opens Ca^{2+} channels in the membrane of the endoplasmic reticulum (step 2), causing release of stored Ca^{2+} ions into the cytosol (step 3). One of various cellular responses induced by a rise in cytosolic Ca^{2+} is recruitment of protein kinase C (PKC) to the plasma membrane (step 4), where it is activated by DAG (step 5). The activated kinase can phosphorylate various cellular enzymes and receptors, thereby altering their activity (step 6). As endoplasmic reticulum Ca^{2+} stores are depleted, the IP_3-gated Ca^{2+} channels bind to and open store-operated TRP Ca^{2+} channels in the plasma membrane, allowing influx of extracellular Ca^{2+} (step 7). [Adapted from J. W. Putney, 1999, *Proc. Nat'l. Acad. Sci. USA* **96**:14669.]


Lumen of blood vessel
Acetylcholine
Acetylcholine GPCR
Phospholipase C
IP_3
Endothelial cells
Ca^{2+}/Calmodulin
NO synthase
Arginine + O_2
Citrulline + NO
NO
NO
GTP
NO receptor
cGMP
Protein kinase G
PP_i
Smooth muscle cells
RELAXATION OF MUSCLE CELL

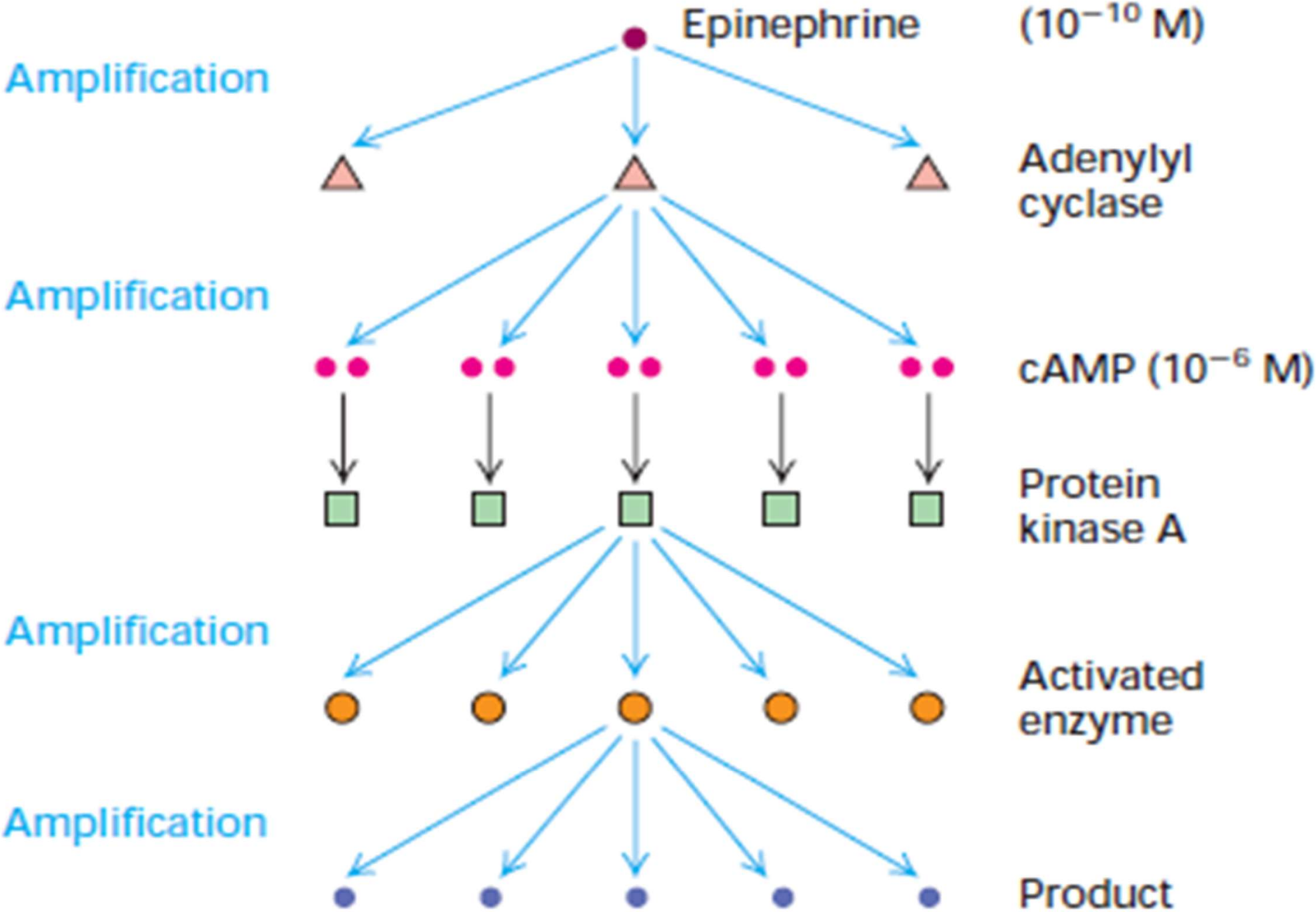

Acetylcholine
Exterior
Cytosol
Active muscarinic
acetylcholine receptor
$G_{\beta\gamma}$
$G_{i\alpha}$
G
D
P
GTP
GDP
K^+ channel
+ +
− −
K^+
+ + + + +
− − − − −
$G_{\beta\gamma}$
$G_{i\alpha}$
G
T
P


(a) Increased cAMP
Stimulation of glycogen breakdown
PKA (active)
Inhibition of glycogen synthesis
GPK
GPK
P
GS
GS
P
Inhibition of phosphoprotein phosphatase
GP
GP
P
IP
IP
P
Glycogen + n Pi
n Glucose 1-phosphate
PP (active)
IP
P
PP (inactive)
(b) Decreased cAMP
Inhibition of glycogen breakdown
PP (active)
Stimulation of glycogen synthesis
GPK
P
GPK
GS
P
GS
GP
P
GP
UDP-glucose
Glycogen + UDP
Abbreviations:
PKA Protein kinase A
PP Phosphoprotein phosphatase
GPK Glycogen phosphorylase kinase
GP Glycogen phosphorylase
GS Glycogen synthase
IP Inhibitor of phosphoprotein phosphatase


NH_3^+
G protein–coupled receptor
Exterior
Cytosol
^-OOC
P
P
AJK-1
β-Arrestin
AP2
MKKY
Clathrin
JNK-1
c-Src
Activation of c-Jun kinase cascade
Endocytosis
Activation of MAP kinase cascade


TNF-α receptor
TNF-α
IL-1
IL-1 receptor
Ionizing radiation
Exterior
Cytosol
1
Unknown mechanism
TAK1
2b
2a
3
p65
p50
I-κBα
P
P
E3 ligase
4
Poly-ubiquitin
α
γ
β
I-κB kinase
Sequestered NF-κB
Free NF-κB
5
Proteasomal degradation of I-κBα
6
7
Induces transcription of target genes
Nuclear-localization signals
Nucleus

► FIGURE 14-28 NF-κB signaling pathway. In resting cells, the dimeric transcription factor NF-κB, composed of p50 and p65, is sequestered in the cytosol, bound to the inhibitor I-κB. Stimulation by TNF-α or IL-1 induces activation of TAK1 kinase (step 1), leading to activation of the trimeric I-κB kinase (step 2a). Ionizing radiation and other stresses can directly activate I-κB kinase by an unknown mechanism (step 2b). Following phosphorylation of I-κB by I-κB kinase and binding of E3 ubiquitin ligase (step 3), polyubiquitination of I-κB (step 4) targets it for degradation by proteasomes (step 5). The removal of I-κB unmasks the nuclear-localization signals (NLS) in both subunits of NF-κB, allowing their translocation to the nucleus (step 6). Here NF-κB activates transcription of numerous target genes (step 7), including the gene encoding the α subunit of I-κB, which acts to terminate signaling. [See M. Karin and Y. Ben-Neriah, 2000, *Ann. Rev. Immunol.* **18**:621, and R. Khush, F. Leulier, and


Epinephrine
(10⁻¹⁰ M)
Amplification
Adenylyl cyclase
Amplification
cAMP (10⁻⁶ M)
Protein kinase A
Amplification
Activated enzyme
Amplification
Product