Signal Transduction

SS 2018

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The Principle of Signal Transduction

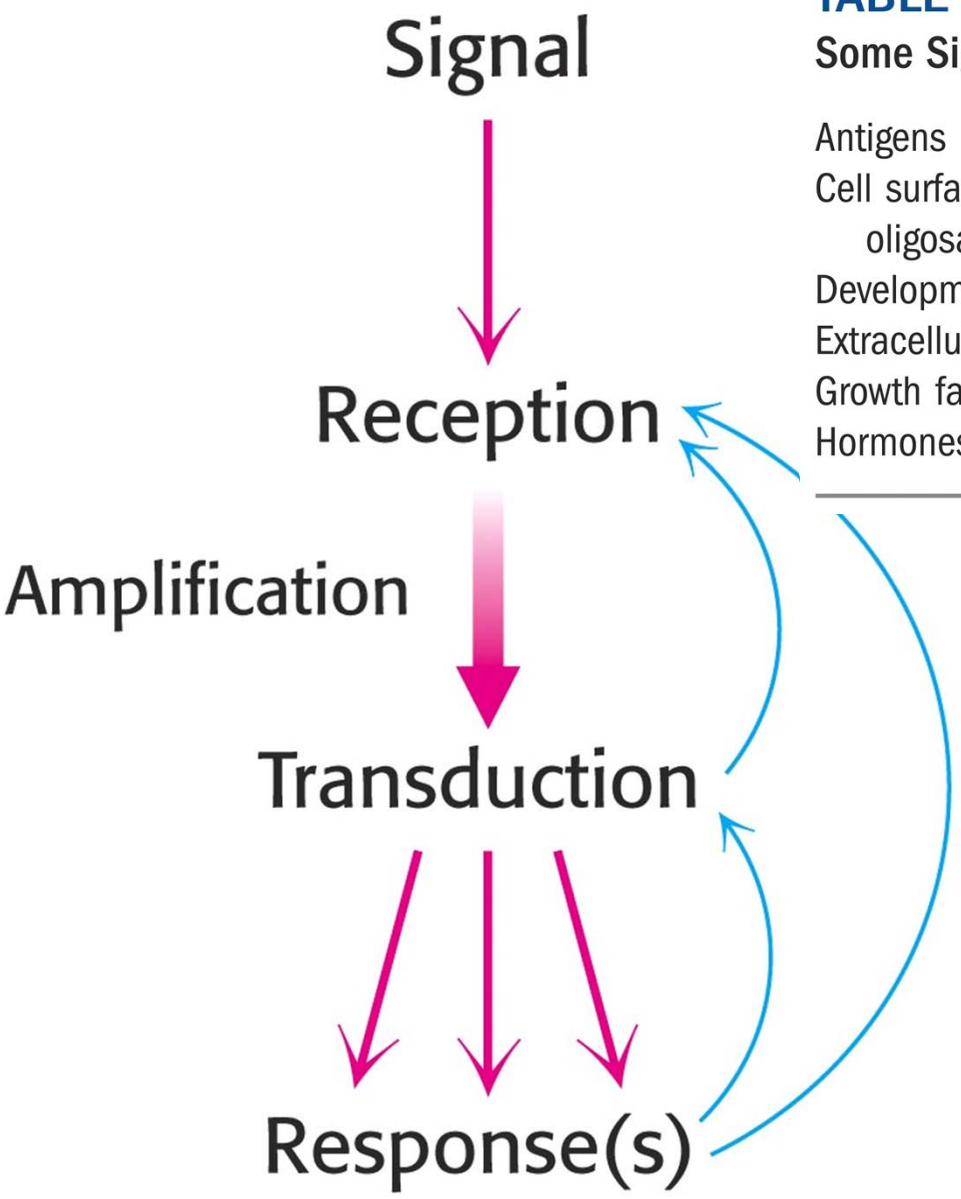

TABLE 12–1
Some Signals to Which Cells Respond

Antigens	Light
Cell surface glycoproteins/ oligosaccharides	Mechanical touch
Developmental signals	Neurotransmitters
Extracellular matrix components	Nutrients
Growth factors	Odorants
Hormones	Pheromones
	Tastants

Some cellular responses:

Differentiation
Proliferation
Migration
Apoptosis

Berg, Tymoczko, Stryer: Biochemistry,

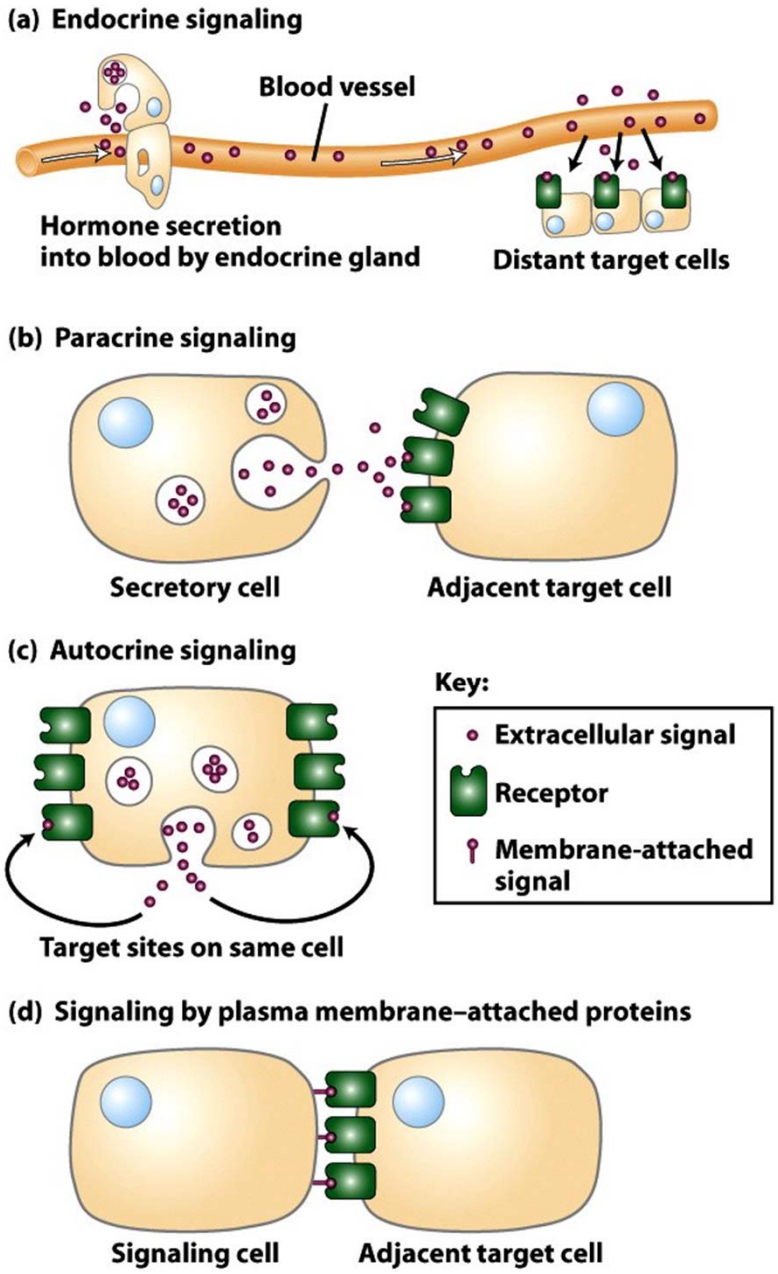

Figure 15-2
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Hormones

Neurotransmitters
Prostaglandines
Growth factors

Growth factor signaling particularly characteristic of tumor cells

Transmembrane proteins

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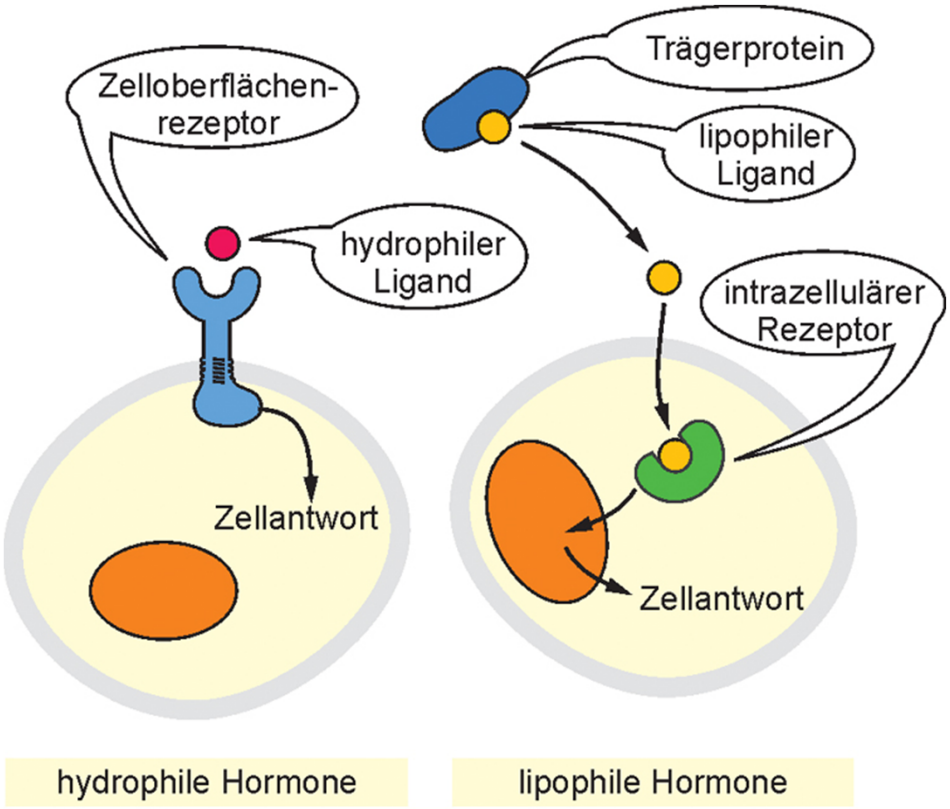
Cellular Receptors



Aus Müller-Esterl, *Biochemie*, © 2004 Elsevier GmbH

Membrane receptors (left) typically have an extracellular domain, the ligand binding site, a transmembrane-segment, and a cytosolic domain, that transduces the signal to intracellular signaling pathways.

Intracellular receptors (right) are located in the cytosol; following ligand binding they are tranferred to the nucleus, where they control gene transcription.

Defining a Receptor

In order for a protein to be classified as a receptor (rather than just a binding protein) several criteria must be fulfilled:

Specificity – a receptor must be able to distinguish between often closely-related signals

High affinity – signals are often present in low concentrations – effective receptors can often detect nM to pM concentrations

Saturability – a cell has a finite number of receptors and, thus there is a limit to the number of ligand molecules a cell can bind

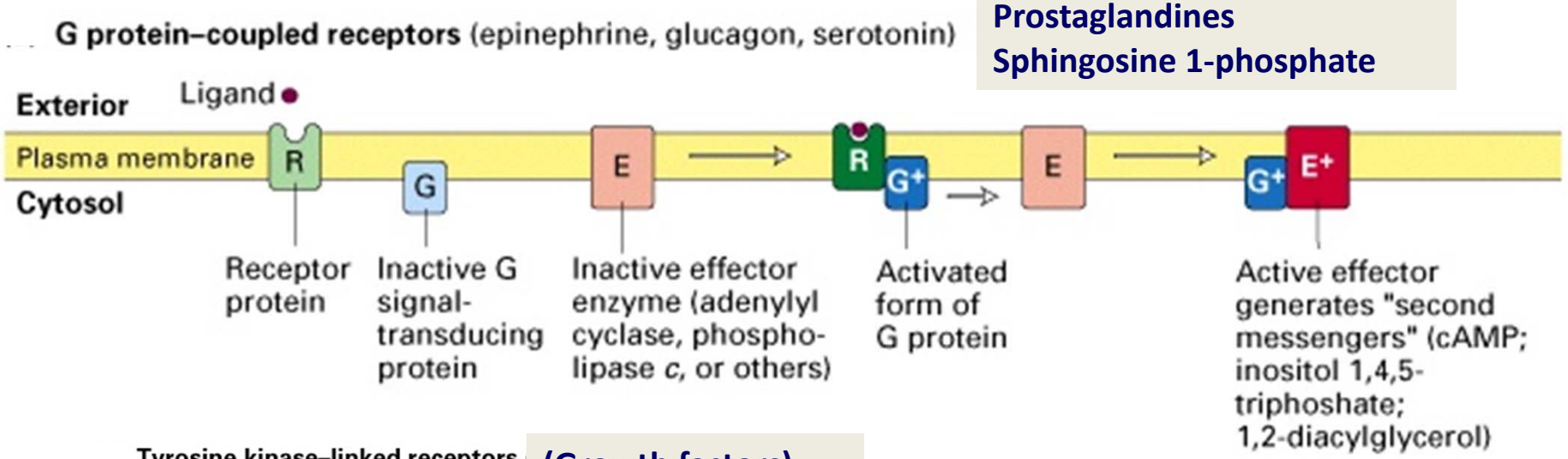
Reversibility – ligand-receptor association is not covalent – as the ligand concentration drops the complex can dissociate

Coupling – the receptor transfers a signal from ligand to cell

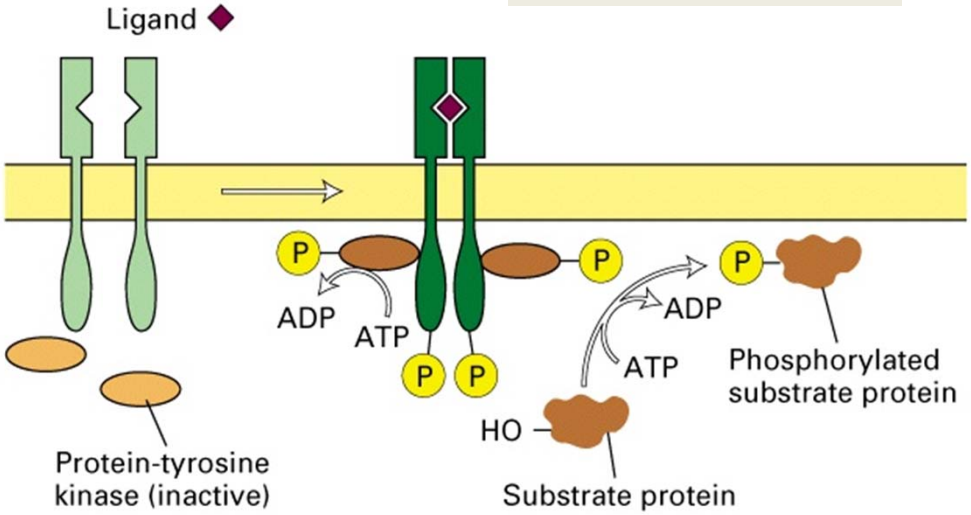
It is this last feature, more than any other that distinguishes a receptor from a binding protein

Focus on 2 classes of cell-surface receptors

Prostaglandines
Sphingosine 1-phosphate



(Growth factors)



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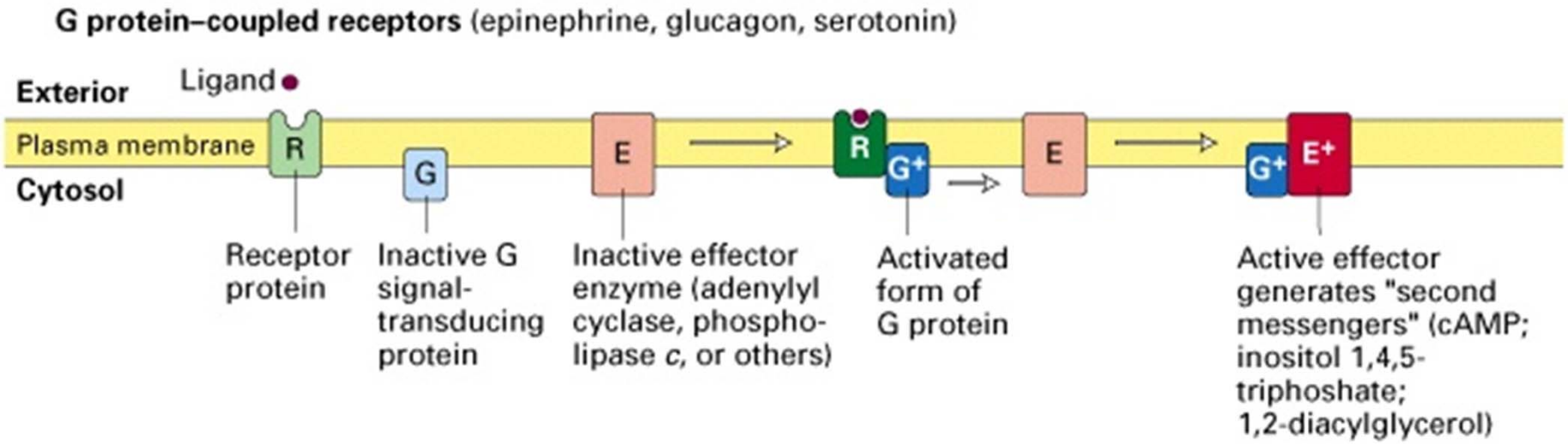
The elements of G protein-coupled receptor systems



- a receptor that contains 7 membrane-spanning domains
- a coupled trimeric G protein which functions as a switch
- a membrane-bound effector protein
- second messengers: amplifier of signal
- protein kinases and phosphatases: propagation of signal

- feedback regulation and desensitization of the signalling pathway

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General structure of G-protein coupled receptors

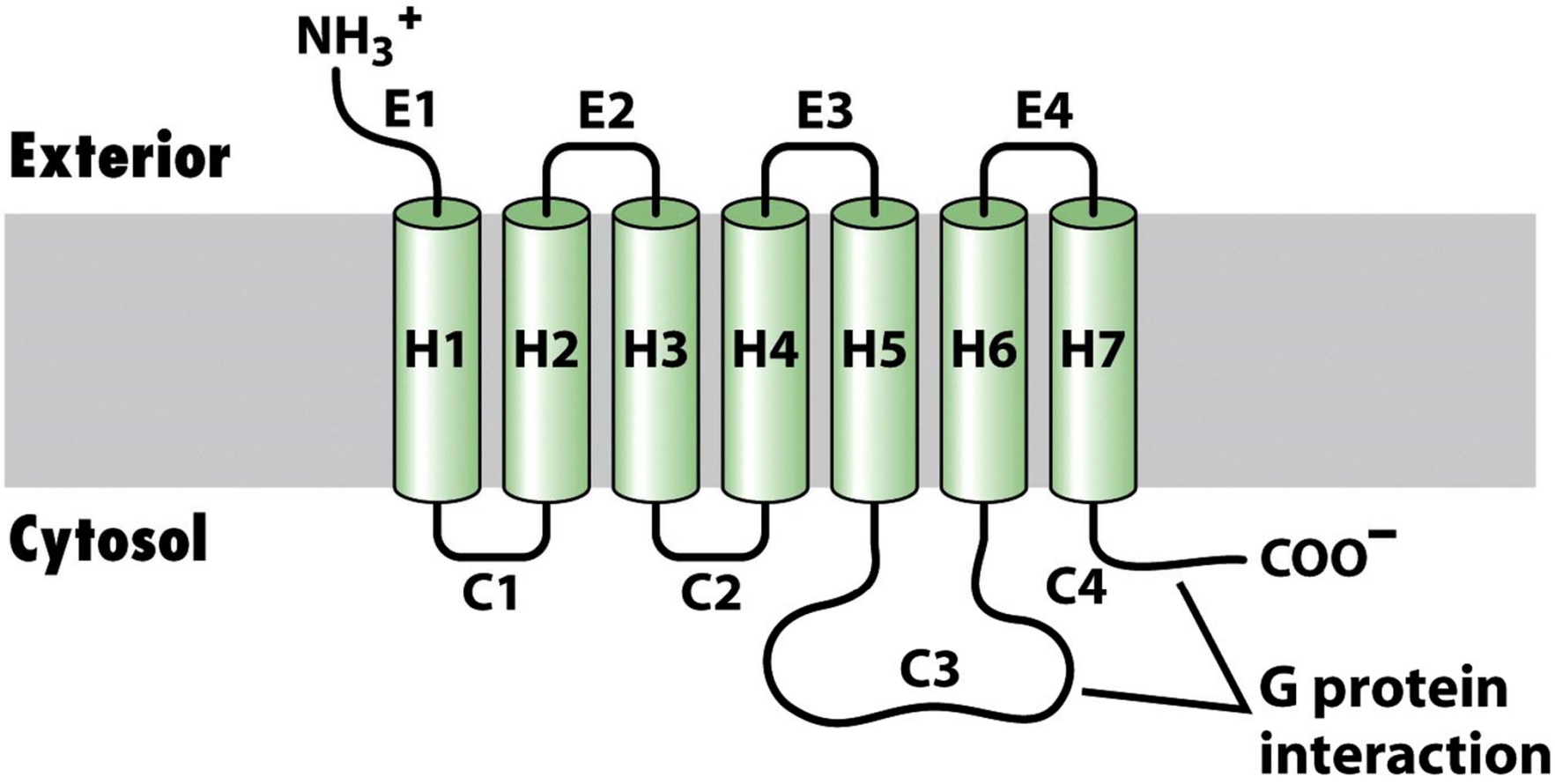

Figure 15-10
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TABLE 15.1 Biological functions mediated by 7TM receptors

- Smell
- Taste
- Vision
- Neurotransmission
- Hormone secretion
- Chemotaxis
- Exocytosis
- Control of blood pressure
- Embryogenesis
- Cell growth and differentiation
- Development
- Viral infection
- Carcinogenesis

Source: After J. S. Gutkind, *J. Biol. Chem.* 273(1998):1839.

Berg, Tymoczko, Stryer: Biochemistry,

Switching mechanism for G proteins

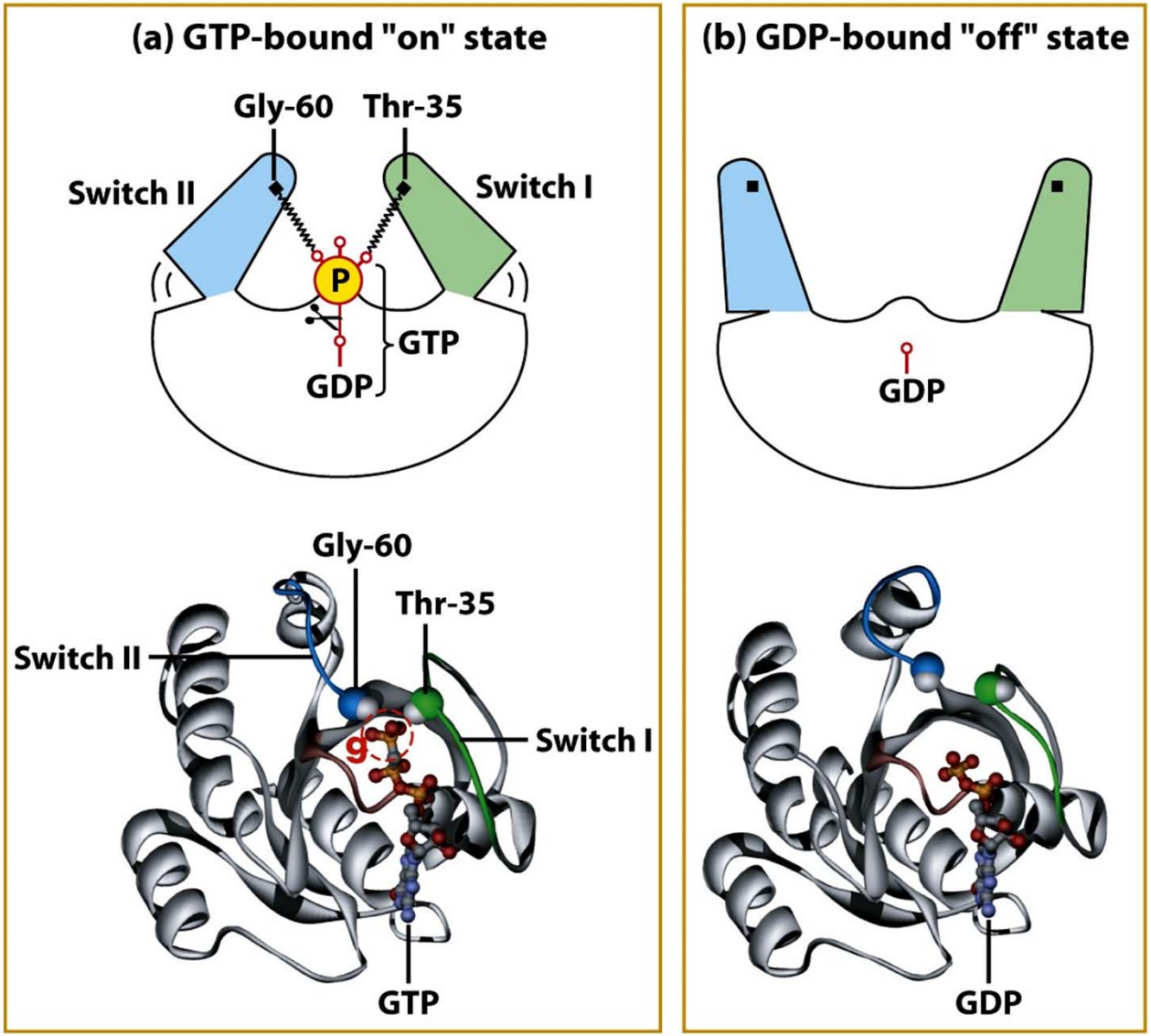

Figure 15-8
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Regulation of the GTPase switch in trimeric G-proteins

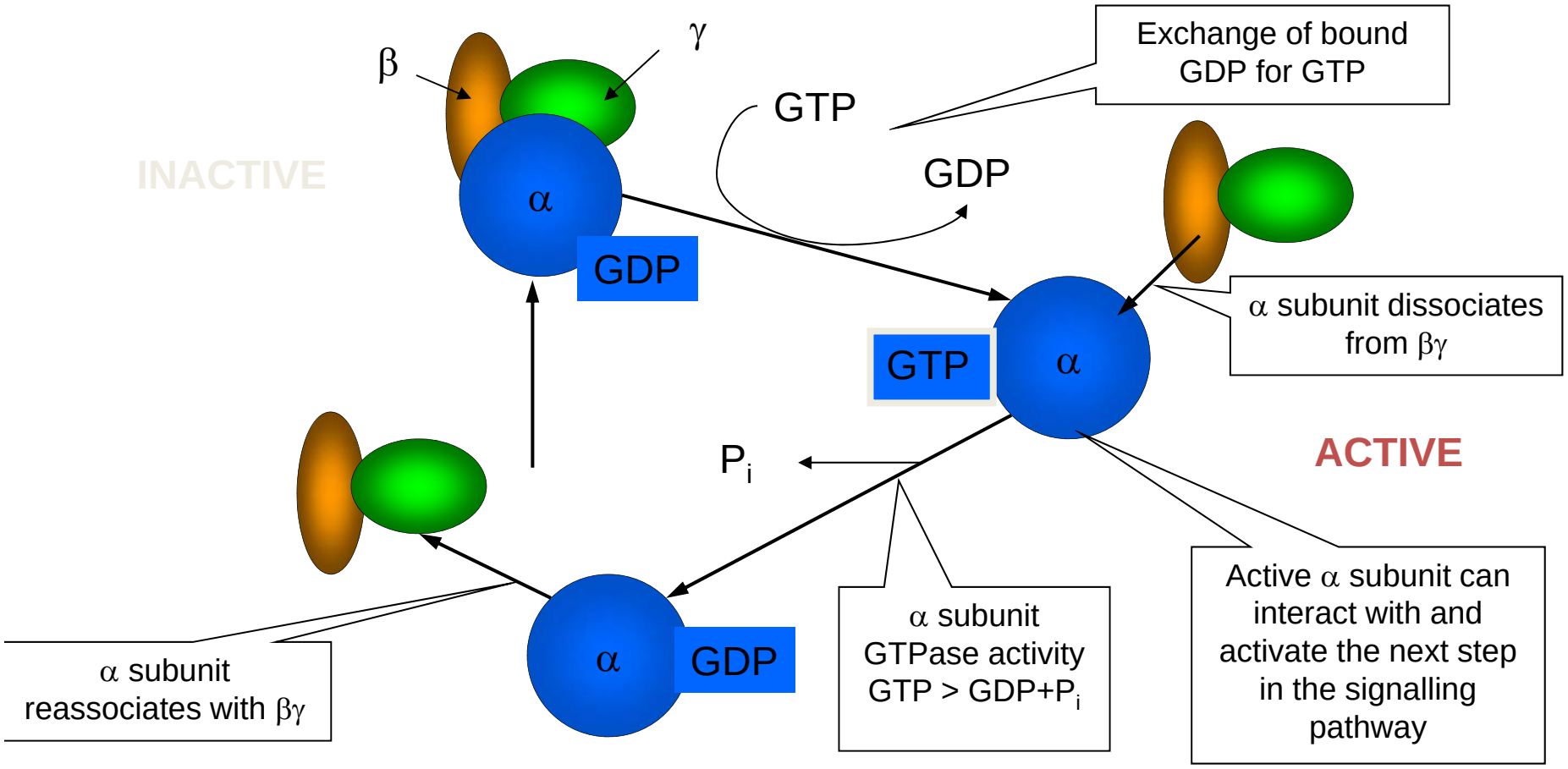
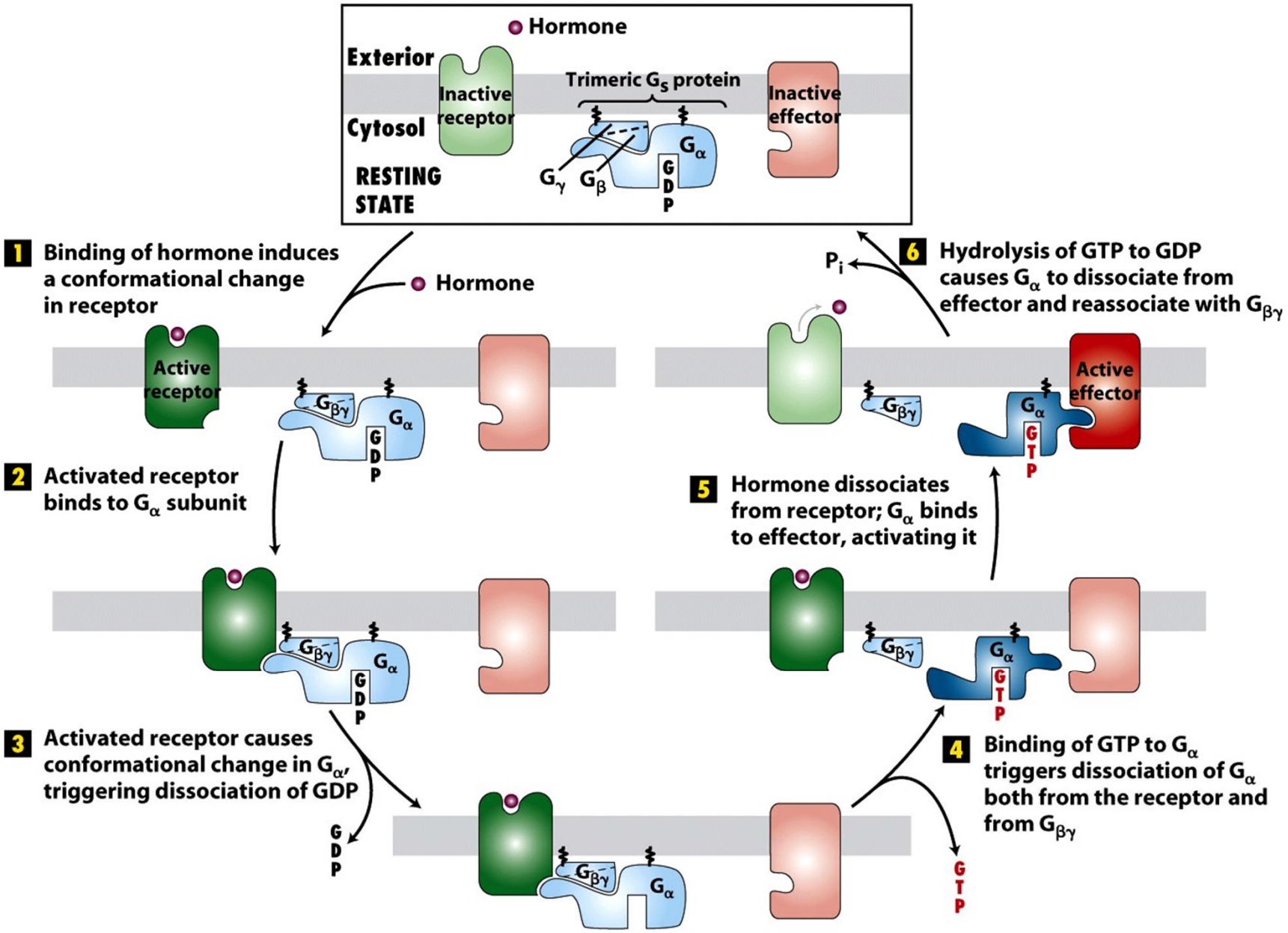


TABLE 15.2 G-protein families and their functions

G_α class	Initiating signal	Downstream signal
$G_{\alpha s}$	β-Adrenergic amines, glucagon, parathyroid hormone, many others	Stimulates adenylate cyclase
$G_{\alpha i}$	Acetylcholine, α-adrenergic amines, many neurotransmitters	Inhibits adenylate cyclase
$G_{\alpha t}$	Photons	Stimulates cGMP phosphodiesterase
$G_{\alpha q}$	Acetylcholine, α-adrenergic amines, many neurotransmitters	Increases IP_3 and intracellular calcium
$G_{\alpha 13}$	Thrombin, other agonists	Stimulates Na^+ and H^+ exchange

Source: Z. Farfel, H. R. Bourne, and T. Iiri. *N. Engl. J. Med.* 340(1999):1012.

Signal transduction from GPCRs to effector proteins



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Effector proteins generate intracellular second messengers

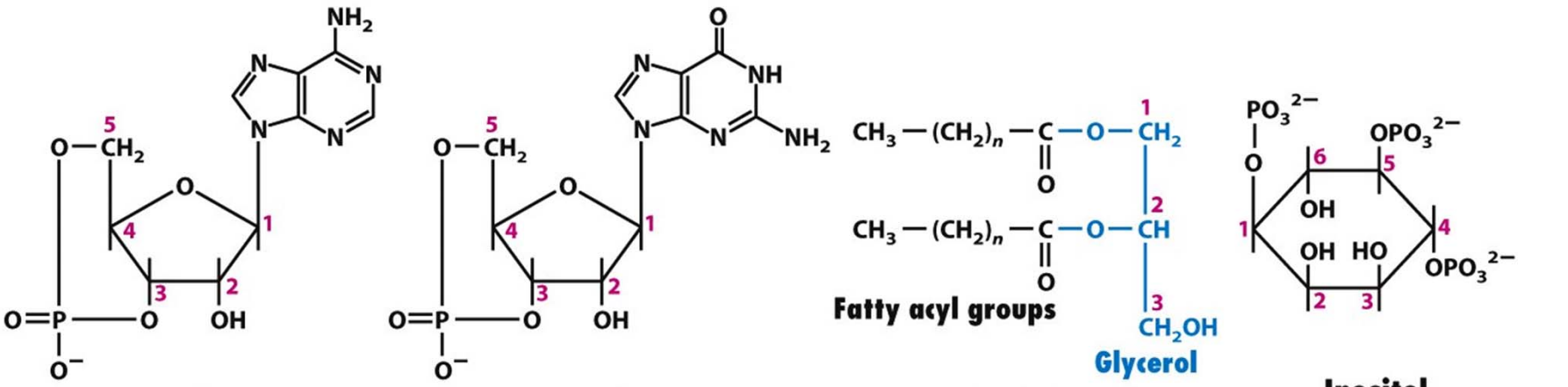

Figure 15-9
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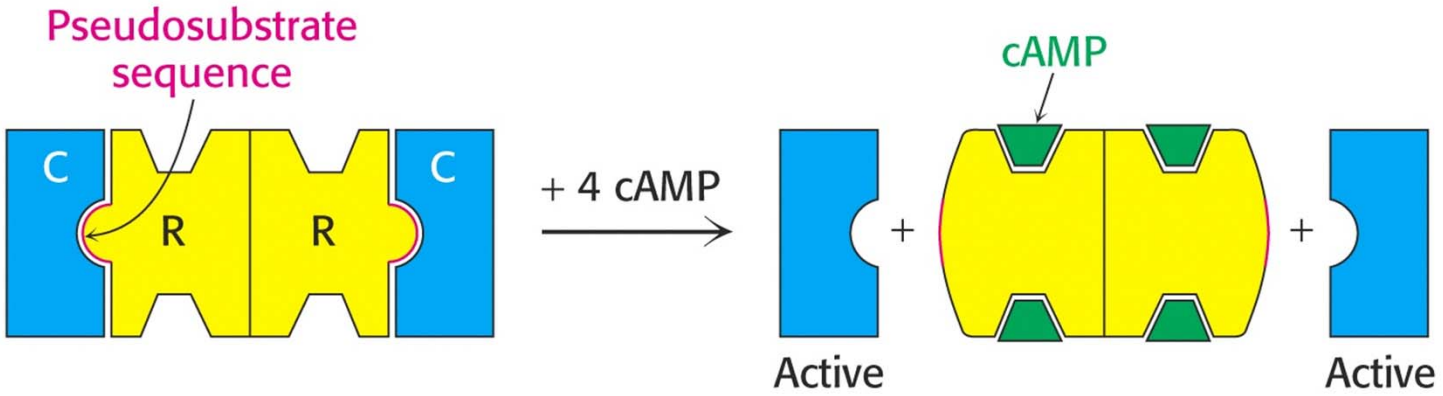
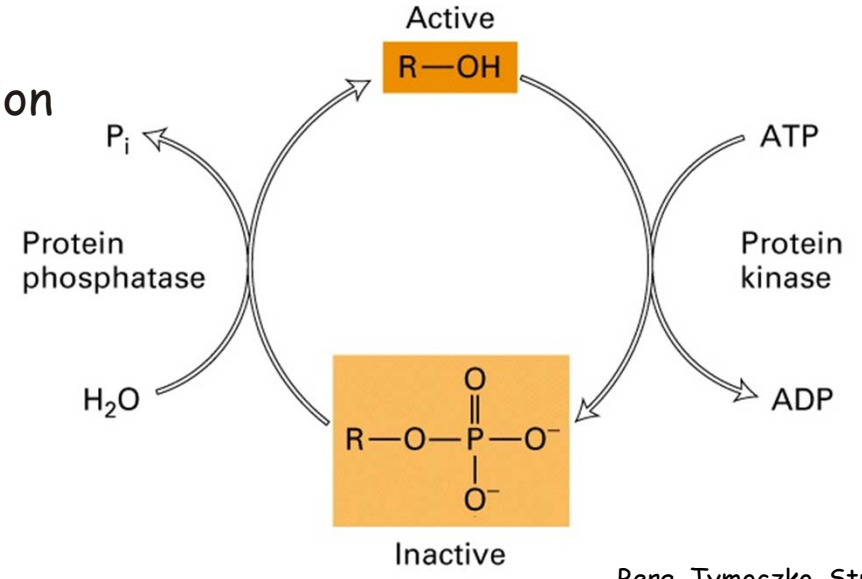
cAMP activates Protein Kinase A



Phosphorylation/Dephosphorylation
highly conserved ON/OFF switch



Berg, Tymoczko, Stryer: Biochemistry,

TABLE 12–3 Some Enzymes and Other Proteins Regulated by cAMP-Dependent Phosphorylation (by PKA)

Enzyme/protein	*Sequence phosphorylated**	*Pathway/process regulated*
Glycogen synthase	RASCTSSS	Glycogen synthesis
Phosphorylase *b* kinase		
α subunit	VEFRRLSI	Glycogen breakdown
β subunit	RTKRSGSV	
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 (cardiac pump regulator)	AIRRAST	Intracellular [Ca^{2+}]
Protein phosphatase-1 inhibitor-1	IRRRRPTP	Protein dephosphorylation
PKA consensus sequence†	XR(R/K)X(S/T)B	Many

*The phosphorylated S or T residue is shown in red. All residues are given as their one-letter abbreviations (see Table 3–1).
†X is any amino acid; B is any hydrophobic amino acid.

TABLE 15-2 Cellular Responses to Hormone-Induced Rise in cAMP in Various Tissues*

TISSUE	HORMONE INDUCING RISE IN cAMP	CELLULAR RESPONSE
Adipose	Epinephrine; ACTH; glucagon	Increase in hydrolysis of triglyceride; decrease in amino acid uptake
Liver	Epinephrine; norepinephrine; glucagon	Increase in conversion of glycogen to glucose; inhibition of glycogen synthesis; increase in amino acid uptake; increase in gluconeogenesis (synthesis of glucose from amino acids)
Ovarian follicle	FSH; LH	Increase in synthesis of estrogen, progesterone
Adrenal cortex	ACTH	Increase in synthesis of aldosterone, cortisol
Cardiac muscle	Epinephrine	Increase in contraction rate
Thyroid gland	TSH	Secretion of thyroxine
Bone	Parathyroid hormone	Increase in resorption of calcium from bone
Skeletal muscle	Epinephrine	Conversion of glycogen to glucose
Intestine	Epinephrine	Fluid secretion
Kidney	Vasopressin	Resorption of water
Blood platelets	Prostaglandin I	Inhibition of aggregation and secretion

*Nearly all the effects of cAMP are mediated through protein kinase A (PKA), which is activated by binding of cAMP.
SOURCE: E. W. Sutherland, 1972, *Science* **177**:401.

Table 15-2
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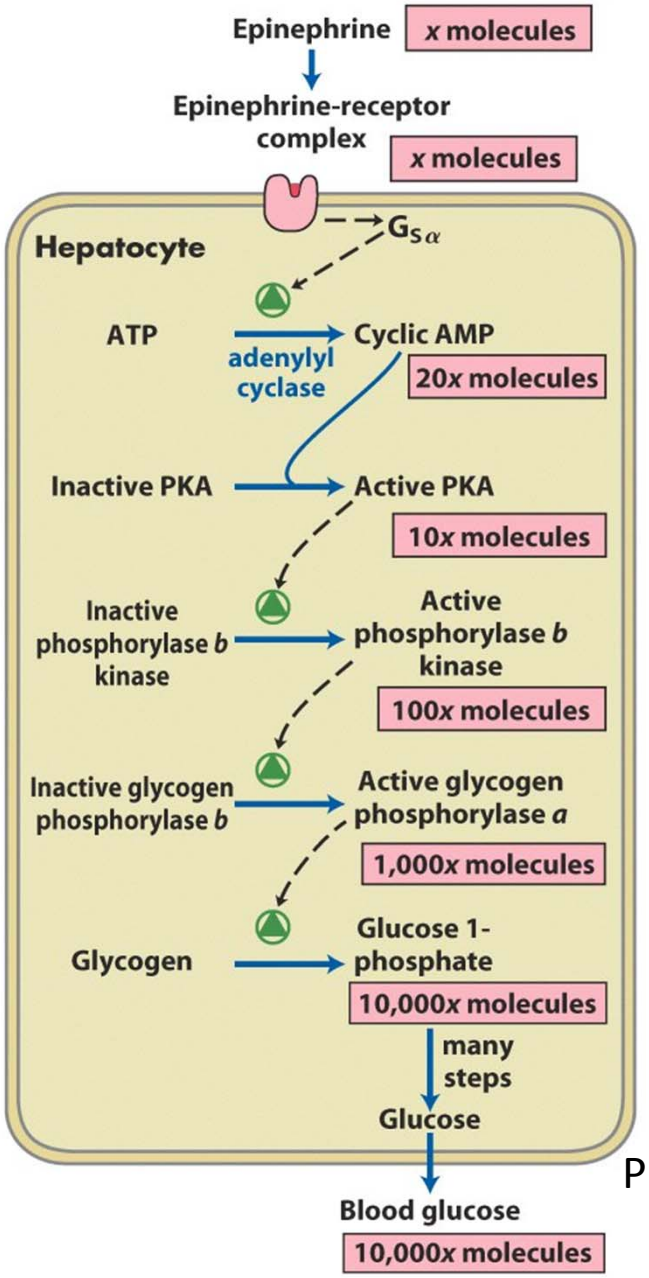
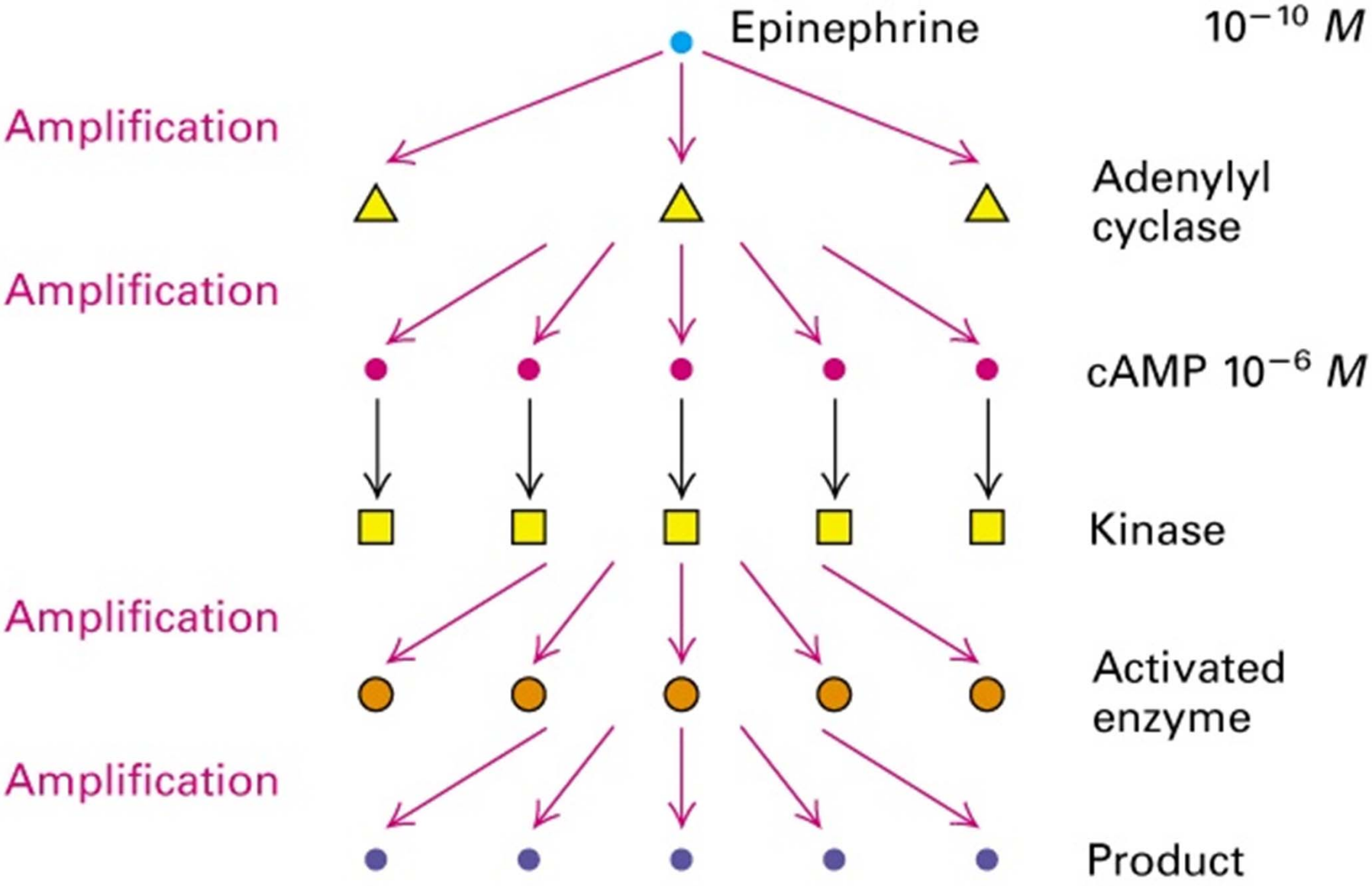
Estimation of the amplification of a hormon-indudced signal



Probably gross underestimation

Nelson, Cox: Lehninger Biochemistry, 2005

Hormon-induzierte cAMP vermittelte Signalübertragungskaskade



Berg, Tymoczko, Stryer: Biochemistry,

The same effector protein is differently modulated by receptors coupled to different G-proteins

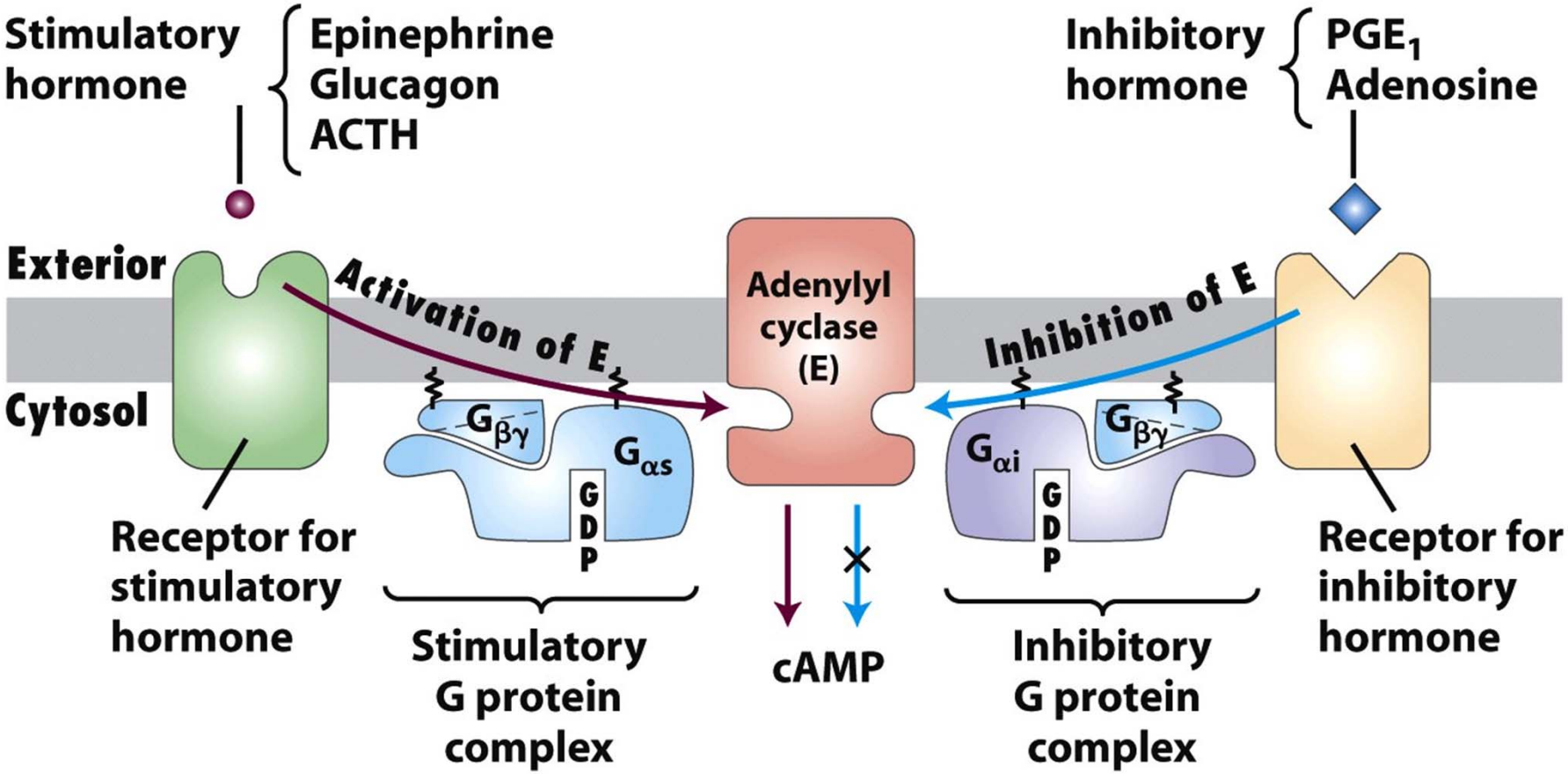


Figure 15-21
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Hormone-induced activation and inhibition of adenylyl cyclase in adipocytes

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TABLE 15.2 G-protein families and their functions

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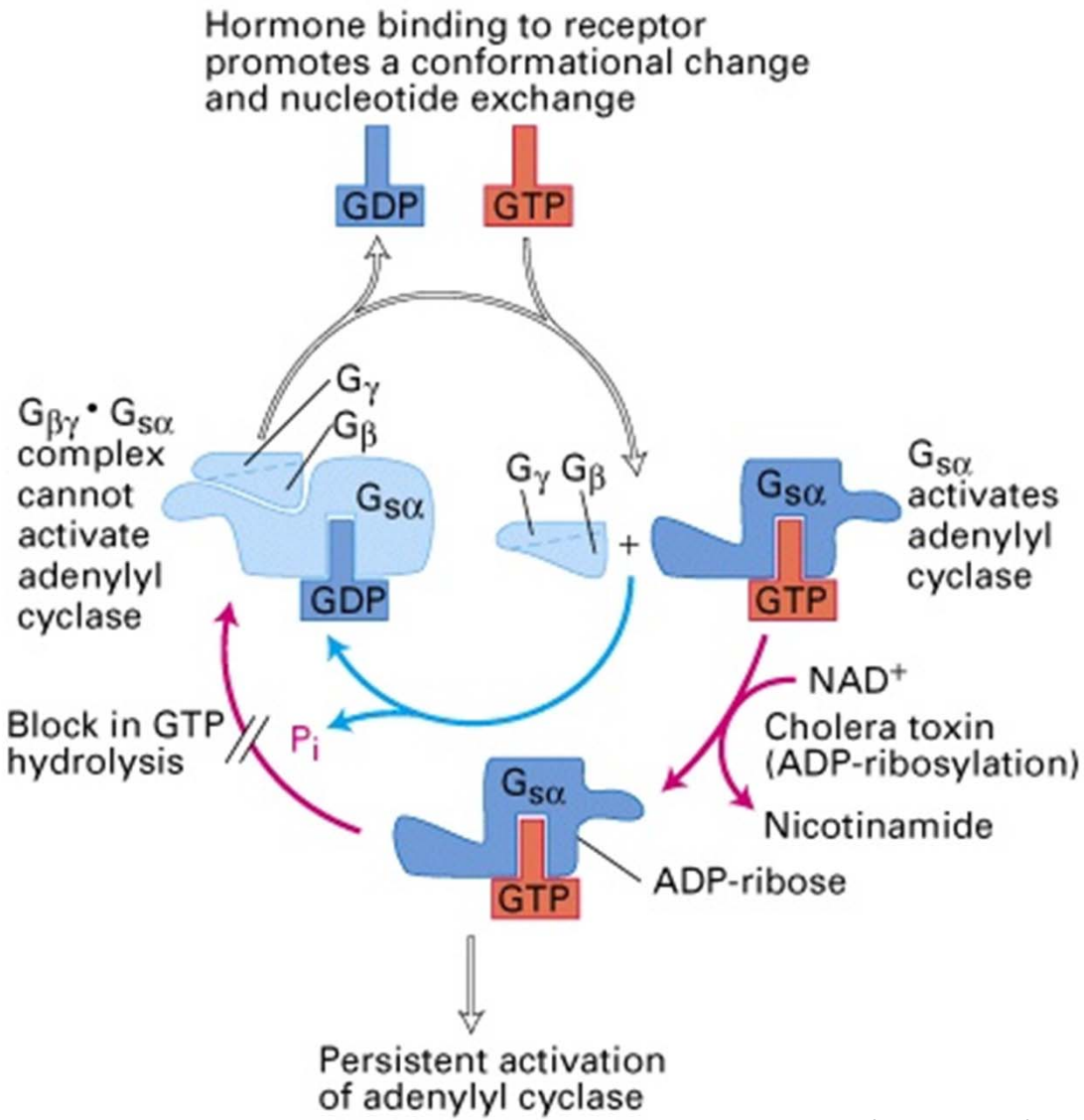
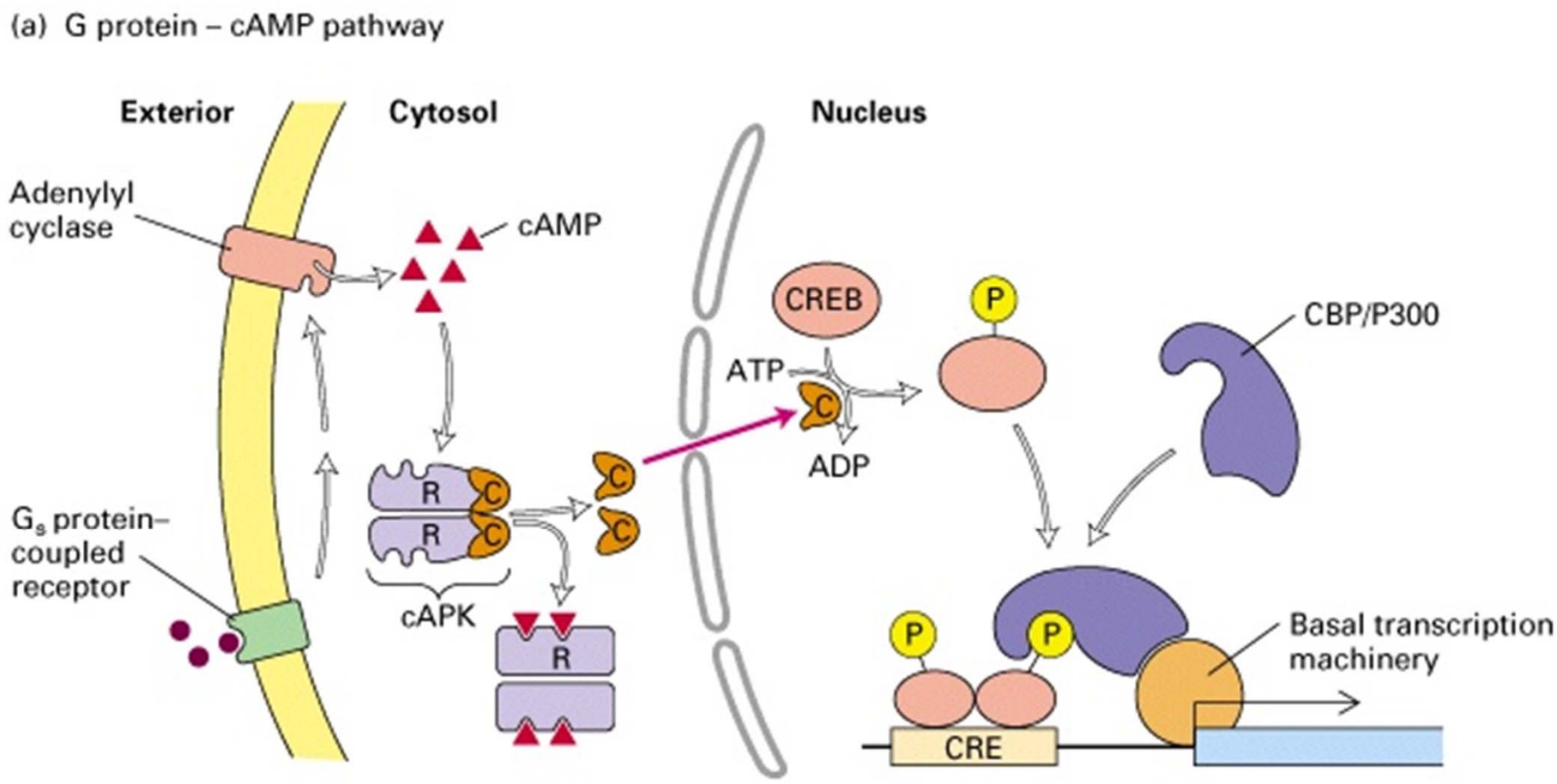
Source: Z. Farfel, H. R. Bourne, and T. Iiri. *N. Engl. J. Med.* 340(1999):1012.

Some bacterial toxins irreversibly modify G proteins



Nelson, Cox: Lehninger Biochemistry,

CREB links cAMP signals to transcription



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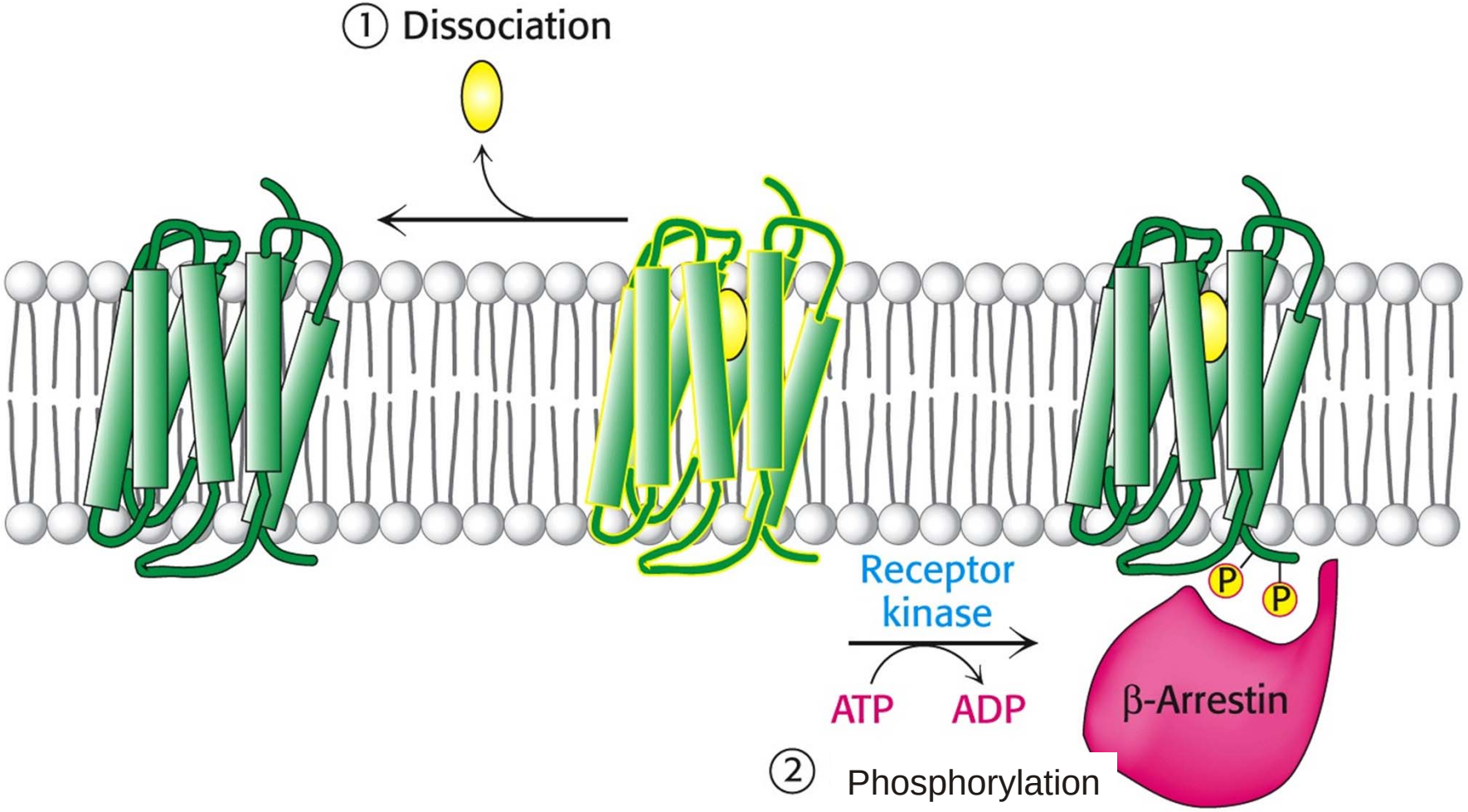
Termination/desensitization of the signal transduction process



3. Phosphodiesterase (PDE) catalyses hydrolysis of cAMP (calcium-dependent)
4. GTP-hydrolysis

Berg, Tymoczko, Stryer: Biochemistry

Role of β-arrestin in desensitization and signal transduction

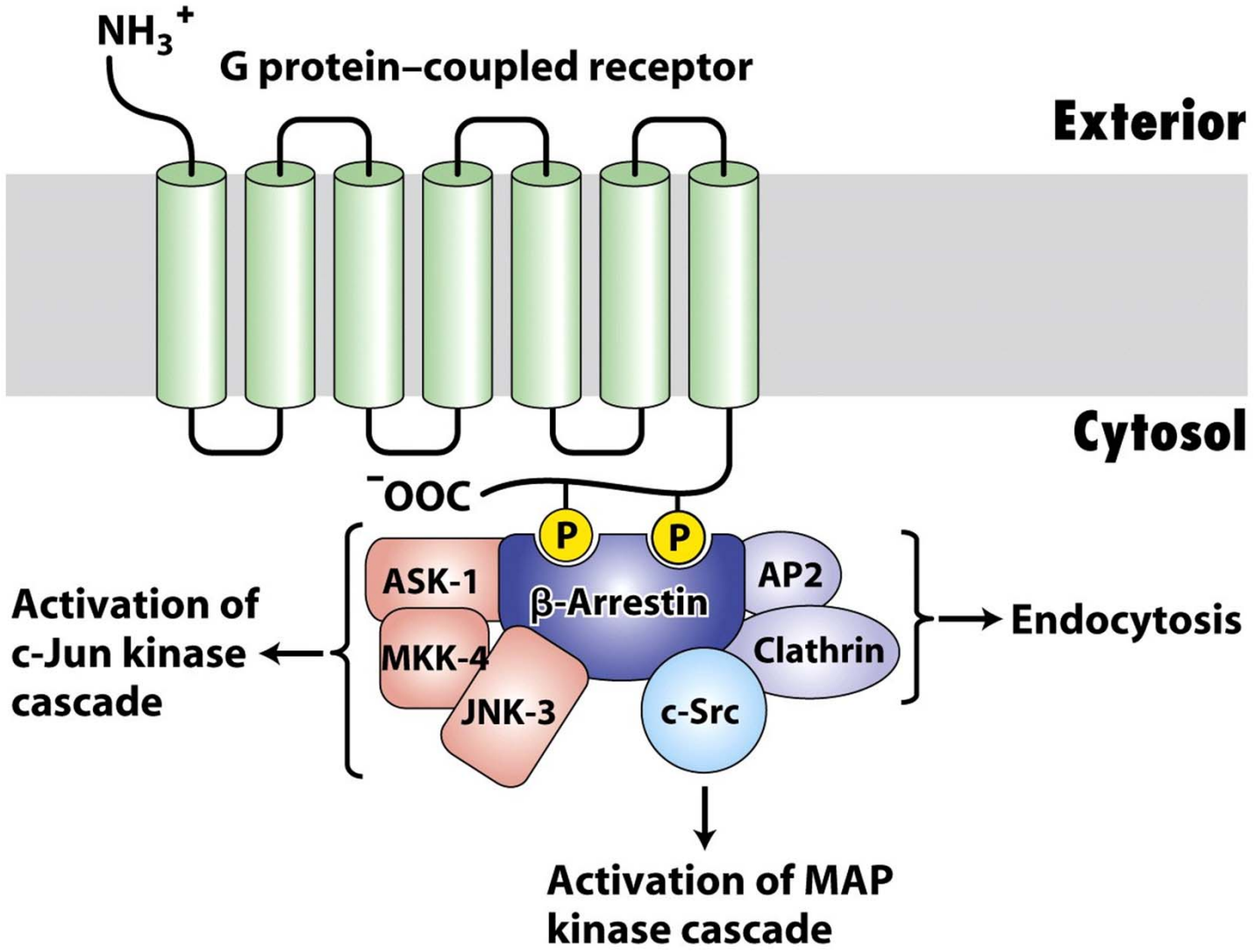


Figure 15-27
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